Clinical Study on Toxicity of Cypermethrin in Arrabi Sheep

A Thesis Submitted to the Council of The College of Veterinary Medicine – University of Basrah In partial Fulfillment of The Requirements for the Degree of Master of Science in Veterinary Medicine (Internal and Preventive Medicine)

By

Hassanin Husham Naser Al-Autaish

B.V.M.S

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Supervised by

Assist.Prof.
Dr.Rahman Kahdum Muhsen

Assist.Prof.
Dr.Israa Abdul-Wadood Alsaad

1431 AH **2010 AD**

بسم الله الرحمن الرحيم

وإن لكم في الأنعام لعبرة نسقيكم مما في بطونه من بين

فرث ودم لبنا خالصا سائغا للشاربين

صدق الله العلي العظيم

سورة النحل – الآية ٦٦

Supervisors confirmation

We certify that this thesis was prepared under our supervision at the department of internal medicine ,surgery and obstetric , college of veterinary medicine / university of Basrah as a partial requirement for the degree of master of science in veterinary medicine – internal and preventive medicine .

Signature
Assist. Prof.
Dr.Rahman Kadhum Muhsen

Signature
Assist. Prof.
Dr. Israa Abdul_Wadood Alsaad

The recommendation of the head of the department

In the view of the available recommendation I forward this thesis for debate by the examining committee.

Signature

Dr. Mohammed Abdul-Hussain Yakoub Al-Aamery
Head of the Dept.Of Medicine
Veterinary Medicine College
University of Basrah

Certification of Examining Committee

We, the members of examining committee, certify after reading this thesis ((***Clinical Study on Toxicity of Cypermethrin in Arrabi Sheep***)) and after examining the student in its contents, we found it is adequate for the award the degree of Master of Internal and Preventive Medicine with very good degree.

Signature
Assistant professor
Dr. Ahmed H.A.Al-Azam
College of Veterinary Medicine
University of Kufa
Chairman

Signature
Assistant professor
Dr. Abdul Razaq N. Khudyer
College of Medicine
University of Basrah
Member

Signature
Lecturer
Dr. Mohammed A . Y. Al-Aamery
College of Veterinary Medicine
University of Basrah
Member

Signature
Assistant professor
Dr. Rahman Kadhum Muhsen
College of Veterinary Medicine
University of Mosul
Member/Supervisor

Signature
Assistant professor
Dr. Israa Abdul-Wadood Alsaad
College of Veterinary Medicine
University of Basrah
Member/Supervisor

Approval for College Committee on graduate studies

Signature
Assistant professor
Dr. Basil Abdul Zahra Abbas
Dean
College of Veterinary Medicine / University of Basrah

Dedication

To my father and mother ….

To my brothers and sisters ....

To my wife who's stood beside me ….

To my daughter Fatima and my son Ali …

I am gifting this job .

SUMMARY

This study was done to determine the effects of cypermethrin (CYP) on clinical signs and some haematological and biochemical parameters and histopathological changes in Arrabi sheep .

The study include two parts : Part I is conducted with the low oral dose of CYP of 17 mg/kg b.w./day administered to 4 sheep (T-group) while other 4 sheep served as control group(C-group) for a comparative studies

Daily observation of clinical signs was made while blood and serum samples collection done every 15 days for the haematological and biochemical examinations. The results revealed that there was no significant difference in mean of temperatures ($P>0.01$), while there was significant increase in the pulse and respiratory rates ($P<0.05$) . There were no significant difference indicated in MCV and MCHC .

In contrast there was a significant decrease in the Red Blood Cells (RBC) count , Haemoglobin concentration (Hb%), Packed cell volume (PCV) and Total protein (TP) ($p<0.05$) in the T-group and there were significant increases in the liver enzymes : Lactate dehydrogenase (LDH) , Aspartate aminotransferase (AST) , Alanine aminotransferase (ALT) , Alkaline phosphatase (ALP) and in kidney functions : Blood Urea Nitrogen (BUN) and Creatinine ($p<0.01$) in the same group .

Then after 63 days of treatment ,the animals of the T-group were killed for the gross and histopathological studies and the results revealed that there was congestion of subcutaneous blood vessels , intestine , kidney , spleen (which appear as dark black color) , liver , mesenteric blood vessels , thoracic cavity blood vessels, brain and trachea. Lungs with grey hepatization was observed,. There was enlargement of mesenteric lymph nodes , kidneys and gall bladder which contain dark

serous fluids as a gross lesions . While brain , cerebellum , medulla oblongata , spinal cord , rumen , abomasum , small and large intestine , lungs , trachea , kidney , liver , testis , heart and bon marrow has a histopathological changes .

Part II , the high single dose of CYP of 70 mg/kg b.w. given to 4 animals , the clinical signs , blood and serum at zero time,6,12 and 24 hours of experiments .The post treated periods compared with the zero time in the hematological and biochemical examinations, the results indicate by : there was no significant difference in the mean of temperatures, RBCs count , Hb% , PCV , MCV and MCHC between the zero time and treating time in all animals until the end of the experiment .While there was a significant increase in the pulse and respiratory rates , liver enzymes which include : AST ,ALT ,ALP and LDH between the zero time and treating time in all animals until the end of experiment,but there was significant decrease in TP .

The animals were killed at the end of experiment to study the gross and histopathological changes .The results revealed that : there was congestion of subcutaneous and thoracic cavity blood vessels. Severe congestion of kidney , brain , lungs (undergo severe congestion with gray hepatization) ,abomasums, large and small intestine with gaseous dilatation of large intestine and enlargement of mesenteric lymph node as a gross lesion . While brain (cerebellum) , medulla oblongata , spinal cord in all it's regions , rumen , reticulum , omesum , abomasum , large intestine , lungs , trachea , kidney , liver and bone marrow have a histopathological changes .

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Chapter One

Introduction

INTRODUCTION

Cypermethrin (CYP) is a synthetic pyrethroid insecticide found in the flower heads of *Chrysanthemum* species (WHO,1989;Cox,1996). It is use for more than 40 years and accounts for 25% of the worldwide insecticide market . (Cox,1996; Khan *et al*.,2009).

Cypermethrin is used for the control of ectoparasites . It consists of a mixture of four cis- and four trans-isomers. The cis-isomers are considered to be more acutely toxic than the trans-isomers. It is used to treat the infested cattle, sheep, poultry and some companion animals (Cox,1996; EMEA,1998,2003,2004).

The main target organ of CYP is the nervous system . It acts on the sodium channel in the nerve membrane by delaying the closing for several seconds (Seth *et al.* ,2000 ; Brown,2005 ; Valez *et al.*2008) .

Because of its rapid absorption , metabolism , wide distribution and slow elimination (Beasley,1999; Beyrbach,2000) , so it is classified as class II in toxicity (WHO,1997; Reigart,1999) . It induce many effects on hematological and biochemical features of the immunological , reproductive , respiratory ,dermatological , muscular, urinary, central and peripheral nervous and digestive systems (Temple and Smith.,1996).

Cypermethrin residues are found mainly in the fat, but also in the liver , kidney , muscles and milk where presents in various concentrations in the ruminants (sheep ,goats, cattle) (Beyrbach,2000 ; EMEA ,1998 ,2003 ,2004)

- **Aims of the Study**

Include study of the following :

a- Clinical signs and determining the toxic signs .

b- Blood parameters : red blood cells count (RBCs count) , haemoglobin concentration (Hb%) , packed cell volume (PCV),

mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) .

c- Liver enzymes activity : alanine aminotransferase (ALT) , aspartate aminotransferase (AST) , alkaline phosphatase (ALP)and lactate dehydrogenase (LDH) .

d- Kidney functions blood urea nitrogen (BUN) and creatinine and study the total protein (T.P.) .

e- The study of the gross and histopathological changes of many organs .

Chapter Two

Review of Literatures

2-1- Definition

Cypermethrin is a synthetic pyrethroid which is applied topically to control of ectoparasites such as lice ,ticks and blowflies in cattle ,sheep ,rabbits ,dogs and poultry.(Roberts,1987 ; EMEA,2004) .It is produced as liquid , semi liquid and powder .(WHO, 1989; Sudakin,2006; USEPA,2010).

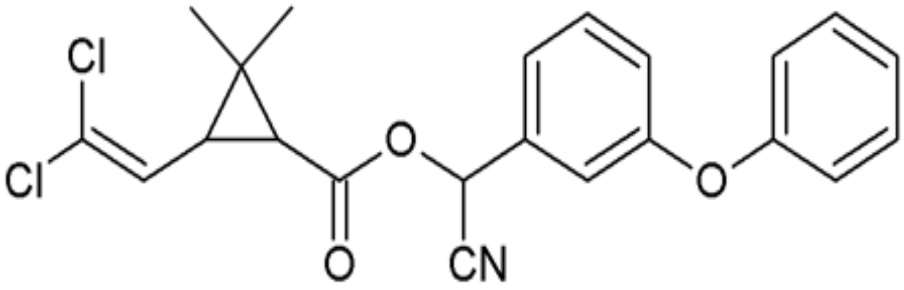
It is widely used in veterinary medicine by dipping ,spraying ,pour-on and spot-on (Harlod *et al*.,2003; Sudakin,2006). It has a high insecticidal activity with a low avian and mammalian toxicity and adequate stability in air and light . It is also important in agricultural uses and plants protection (Vijveberg and Vanden Braken ,1990;Baker *et al* ,2007).

2-2- Classification of pyrethroids

Cypermethrin is one of the synthetic pyrethroids which are synthesized chemicals modeled on the natural pyrethrin molecule (Harlod *et al*.,2003;Yilmaz *et.al.* 2008).The chemical classes of pyrethroids are divided into two structurally related subclasses . Type I represents ester bond pyrethroids without α-cyano-reside and includes :allthrin , bioallthren , peremethrin , phenothrin , resmethrin and tetramethrin ,while type II includes all ester bond pyrethroids containing α- cyano-group at the α-carbon atom which includes alphacypermethrin , cypfluthrin , cyhalothrin , **cypermethrin** , deltamethrin , fenvalorate , flumethrin and tau-fluvalinte (JECFA,1997,2000) , cypermethrin have cis and trans isomers (Roberts,1987 ; Wefco,1989; Sudakin,2006).

2-3- Chemical and Physical Characteristics

Table (2-1) Chemical Identifications :

- Common name	**Cypermethrin (CYP.)**
- Chemical name	**(RS) –alpha-cyano-3-phenoxybenzyl-(1RS,3RS,1RS ,3RS)-3-(2,2-dichlorovinul)-2,2-dimethylcyclopropane carboxylate .**
-Chemical Abstracts) Name	**(RS)-cyano(3-phenoxyphenyl)methel(1RS)-cis-trans-3(2,2-dichloroethenyl)-2,2-dimethylcyclopropan carboxylate .**
-Cypermethrin is a mixture of all eight possible chemical isomers	
Structural formula	**C22H19Cl12NO3**
Molecular weight	**416.3 D**
-Chemical structure	**CH3 CH3** 

According to (Roberts,1987 ; Vijverberg and Vanden Braken,1990 ; Atamanalp *et al.*,2002 **).**

Table (2-2) Physical Properties :

-Appearance	**Yellow –brown viscus liquid to semi-solid crystalline mass**
-purity	**The commercial preparation 94.2% CYP.**
-Melting point	**80.5 °C**
-Vapor pressure	**1.9×10^{-7} Pascal at 20 °C**
-Solubility g/L at 20 °C **Water** **Cyclohexane** **Xylen** **Ethanol** **Hexane**	**9.0×10^{-6}** **>600** **>600** **>337** **103** **>450**
-Density	**1.23Kg / L at 20 °C**
-Octanol-water partition coefficient (p)	**20×10^{-6}**
-Stability: **Hydrostatic** **Photolytic** **Thermal** **Oxidation**	 **Stable under acid or natural conditions but not alkaline conditions .** **Stable** **Stable to 220 °C** **Stable in air at ambient temperatures .**
-Avarge of 3pH 's at 20 °C	**2.5×10^{-7} at m-m^3 /mol**

-Soil adsorption coefficient (Koc) (average of data for five soil types)	**$6.1X10^{-4}$ ml /g .**
-Aerobic half -life	**$6 X 10^{-20}$ days**
-Anaerobic half –life	**<14 days**

According to (Roberts,1987 ; Vijverberg and Vanden Braken,1990 ; Atamanalp *et al.*,2002 **).**

2-4- Cypermethrin History and Uses

The natural pyrethrin family is derived from the chrysanthemum flowers ; it contains about 25 % of pyrethrins .(Tamang *et.al.*,1991; Cox ,1996 ; Harlod *et al*.,,2003) . Cypermethrin is widely used through the world over 40 years since the late 1970 s. (Yousef *et al* ,1998 ; C.A.C. ,2003).

In Iraq the insecticide makes up approximately 80% of the imported pesticide every year.(Heamza,2009). But more than one billion pounds of pesticides are used each year in USA alone . In Egypt large quantities of pesticides (more than 30,000 metric tone of related pesticides) are imported and used annually (Yousef *et. al.* ,1999). CYP. composed about 25% of the pesticide world market .(Khan *et al* ,2009) Over ninety percent of the CYP manufactured worldwide is used to kill insects (ticks , lice , manges) either by dipping or spraying (Harlod *et al*.,,2003).

Also it is used in household treatments and it persists in the air ,on walls and furniture for about three months . Among structural pest control operators in California it is the fourth most common cause of pesticide – related illness (Cox ,1996;Hill *et al*.,2010). Now it is widely used in plants protection (Vijverberg and Vanden Braken, 1990 ; Knisel,1993; Baker *et al.* , 2007).

2-5- Mode of Action

The main target organ of CYP is the nervous system (Tamang *et al*.,1991; Narahashi,1996;Brown , 2005; Edward,2006: Flaskos *et.al.*, 2006; Crane *et al*. ,2007 and Anynomous,2010). It is directly acts on the sodium channel (JECFA,1997,2000; Beasley,1999; Seth *et al*. 2000; Valez *et al*,2008) . CYP affects the sodium channel by slowing the closing of the channel for several seconds (Wefco,1989 ; Tamang *et.al*.,1991; Smith *et al*,1996; Tample and Smith,1996 ; Reigart *et al*,1999) . (Narahashi,1996; Beasley,1999) report that the peak sodium conductance is decreased by prolonging the sodium conductance and suppressing potassium conduction then the action potentials and repetitive nerve discharge are decrease ; so that the nerve may be blocked.

Beasley (1999) and Tucker *et al*.(1984)mentions that CYP may inhibit various adenosine triphosphat (ATP) including calcium ATPase and the calcium-magnesium ATPase in the nerve tissue . But another view shows that CYP. affects binding at the acetylcholine nicotinic receptors .

Kol *et al*. (2007) explain that the CYP acts on the nervous system as a cholinesterase inhibitor .the inhibition of cholinesterase activity leads to accumulation of acetylcholine at synopses causing stimulation over of both central and peripheral nervous system .So the exposure will interfere

with the synoptic transmission peripherally at muscarinic and nicotinic receptors .

2-6- Pharmacokinetics

2-6-1- Absorption

CYP is rapidly absorbed from the gastro- intestinal tract (GIT) after oral administration (Roberts,1987 ; Tample and Smith,1996 ; Smith *et al* ,1996 ; WHO,1996 ; Beyerbach,2000 ; Adriana , 2004) and there is also absorption through the gut and pulmonary membrane (Reigart, 1999 ; Khanna , 2002 ; Valez *et al*, 2008 Hill *et al*.,2010) .

A single dose of 3.3 mg (cis : trans ratio 50:50) of Soya oil administrated orally . CYP absorption isbetween 27 – 57 % of the administered dose (Smith *et al* ,1996 ; Tample and Smith, 1996) .

While, the absorption through the skin is not easy (Reigart,1999; Valez *et al*.,2008) that is why the dermal absorption is very slow (Roberts,1987 WHO, 1996 ; Beyerbach,2000 ; Adriana,2004) .

2-6-2- Distribution

The CYP distribution is studied in several mammalian species where it is rapidly and widely distributed to many tissues including the lipid , central and peripheral nervous tissue , liver , kidney , but it is concentrated in the lipid and central nervous tissue (Roberts,1987; Tamang *et.al*.,1991; Khanna,2002) . Smith *et al*.(1996) and Tample and Smith,(1996) indicated that CYP reached adrenal and ovaries tissues too .

The distribution in the nervous system is very rapid with concentration reached peak levels within 5 minutes after the intravenous administration in rats (Roberts,1987; Tamang *et.al*.,1991; Iwanika *et al*.,2008) .

2-6-3- Metabolism

CYP metabolism in mammals is rapid (Atamanalp *et al*,2002) . The CYP metabolism in animals occurs through the ester hydrolysis , oxidation and conjugation (Smith *et al* ,1996 ; Tample and Smith ,1996) . This rapid hydrolysis of the ester linkage in the digestive tract results in the low oral toxicity (Beasley,1999) .

The biotransformation occurs through the hydrolysis of the central ester bond . Oxidation happens at several sites and the conjugation produces a complex array of primary and secondary water-soluble metabolites that undergo a urinary and biliary excretion (Tamang *et.al*.,1991)

CYP and individual isomers undergo hydrolytic cleavage of the ester bond, then followed by oxidation to yield carboxylic acid and phenoxybenzoic acid derivatives . These metabolites are excreted as alcohols ,phenol , carboxylic acid and their glycine , sulfate ,glucouronid , or glucoside conjugates (Roberts,1987; Tamang *et.al*.,1991; WHO,1996; Beasley,1999;EMEA,1998,2003,2004;Carne *et al*, 2007). No information is available about sex or age relationships with the cyp. metabolism in animals (Roberts,1987; Tamang *et.al*.,1991; Beyerbach, 2000) .

2-6-4- Excretion

The oral administration of CYP 3.9 mg /kg shows rapid elimination : about 61 % of this dose at 48 hours (41 % by urine and 20.5 % feces) . (Roberts1987; WHO,1996; Beyerbach,2000 ; Adriana *et al*,2004)**.**

When CYP applied dermally in sheep at a dose of 2.5 % it is eliminated in urine and feces in 6 days . After the oral administration , about 60 % is eliminated in 2 days .(Tamang *et.al*.,1991;Carne *et al*

2007). In rats , the oral dose of CYP 3.3mg /kg as Soya oil base is excreted with peak excretion rates between 4-8 hours after dosing (Tample and Smith ,1996).

In cows, two groups of lactating cows are separately administered CYP twice daily in dose of 0.2 and 10 mg /Kg of feed . The results show that the urine and feces are equally major routes of elimination and only fraction of the percent of the dose appears in the milk (Roberts1987; Woolen *et.al*.,1992) .

Other experiments were conducted on rats ,chickens, sheep and cows yielding similar results except for the milk .where is less than 1 % is excreted .(Tamang *et.al*.,1991 ; Carne *et al*, 2007).

Generally , the topical application of CYP has a slow elimination , for example CYP applied topically at a dose of 21.9 mg / kg on sheep ; less than 0.5 % of the dose is excreted at 42 hours and only 2% is excreted after 6 days later via the urine ,while 0.5 % is excreted at 6 days later through the feces ,but about 30% of treated sheep is found to be healthy (Roberts1987; WHO,1996; Beyerbach,2000 ; Khanna,2002; Adriana,2004; Virouvet *et al*.,2006) .

2-7- Toxication

2-7-1- Lethal Dose (LD50)

There is no stable or standard LD 50 in each species of animals treated with CYP in the experiments .The LD50 differs in each species of animals depending on :

1- Cis - trans isomers ratio .

2- The vehicles used for formulation .

(He *et al*.,1989; Dorman and Beasley,1991; Cox,1996;Tample and Smith, 1996; Jagvinder *et al*. ,2001).

However, the toxic responses in all species are found to be similar (Tample and Smith,1996; Venkateshwaralu *et al*.,1997; Jagvinder *et al*. ,2001). Due to these reasons views on the lethal dose vary according to the searchers and investigators :

Smith *et al*,(1996) show that the oral LD50 of CYP in rats is 187-326 mg/kg b.w in males and 159-500 mg/kg b.w in females rats ,but in mice , it is82-779 mg/kg bw.

The dermal exposure LD50 is 1600 mg /kg b.w in rats while it is more than 2000 mg /kg in rabbits .

Ecobichan(1991) reported that in rats , the oral LD50 ranges between 200-2600 mg/kg bw and in mice, it is 370 mg/kg b.w.

EMEA(1998,2003,2004) reported that the experimental studies of CYP in cis – trans ratio 90 : 10 in corn oil show that the LD50 is 367 mg / kg in females rats and 891 mg / kg in a ratio of 40 : 60 cis – trans isomers.

Crane *et al*. (2007) reported an approximate corresponding of the oral LD50 in rats and mice which is between 82 – 4000 mg / kg .

EPA(1998) saied that the LD50 in rats is found as follows :

-Orally 263 mg/kg b.w

-Dermally 2460 mg/kg b.w

-Inhalation LC50 is 2.5 mg /liter (L).

Tample and Smith (1996) show that the oral toxic dose in mammals is greater than 100-1000 mg/kg . In rats, it was between 160 - 300 mg/kg in cis which is higher than trans isomers >2000 mg/kg .

PMEP (1989) explained the LD50 in rats 247(187-326) mg/kg in males and 309 (150-500)mg/kg in females while the dermal LD50 in rabbits is >2460mg/kg and primary dermal irritation is 0.71 . The subchronic oral dose in rats No Observed Effects Level (NOEL) is 75ppm for pharmacological effects . The NOEL is 150 ppm for toxic

effects . Chronic toxicity in rats NOEL was 150 ppm and Low Observed Effects Level (LOEL) was 500 ppm .

Wefco(1989) saied the oral LD50 in rats is >4150 mg/kg and in mice >138 mg /kg . The dermal in rats is >4920 and in rabbits >2460mg /kg b.w. The inhalation dose in rats is >2.5 mg/l for 4 hours .

2-7-2- Cypermethrin Toxicity

CYP is classified as class II in toxicity. Pesticides that contain CYP bear the signal word CAUTION or WARNING on the product label (He *et al*.,1989,Ecobichan,1991;WHO,1997; Reigart,1999) .

Toxicity depends on several factors such as age , animal species , environment , cis – trans isomers ratio , and vehicles used (Venkateshwaralu *et al*.,1997; EMEA,1998,2003,2004 Amelotti *et al*.,2009) . Synthetic pyrethroids are 1000 times more toxic to wildlife than their predecessor chemicals (VMD,2010) . The toxicity become low after oral administration because of the hydrolysis of the ester linkage in GIT (Beasley,1999) .

2-7-2-1- Acute Toxicity

CYP is moderately toxic in case of dermal absorption or ingestion (Wefco,1989;Temple and Smith,1996;WHO,1996;FMC,2003). The signs of toxicity appear within a few hours following Oral administration and survivors recover within 3 days (Tample and Smith,1996 ;WHO,1996; -Yilmaz *et al*.,2004) .

Dermally the observed signs of a high dose include ataxia , gait abnormalities , tip-toe walking , salivation ,lacrimation , tremors , colonic convulsions , numbness ,tingling ,itching , burning sensation , loss of bladder control , in coordination , seizures and possible death (Smith *et al*.,1996;Shah *et al*,2007). CYP have adverse effects on the central

nervous system (CNS) (Hayes and Laws,1990 ; Chapman *et al*,1993 ; IPCS,1995 ; Tample and Smith,1996 ; WHO,1996 ; Reigarts,1999 ; FMC,2003 ; Crane *et al*,2007 ; Kol *et al*.,2007). Surviving animals recover within 7 days .(Smith *et al*.,1996; Sarkar *et.al*.,2005;WHO,1996).

As for respiratory effects many clinical symptoms have been recorded including shortness of breath , cough and pulmonary edema (Tample and Smith,1996) . After the dermal contact, CYP produces skin sensory effects ,transient itching and tingling sensation .(Tample and Smith,1996;Shafer *et.al*.,2005) .Dermatological effects including transient red papules , congestion and edema of skin have been reported by (Smith *et al*,1996; Tample and Smith.,1996;O'Malley,1997).

The signs of a high dose ingestion include nausea , prolonged vomiting , abdominal pain and diarrhea which progresses to convulsions ,unconsciousness and coma (Wefco,1989 ; Hayes and Laws,1990 ; Reigarts,1999 ; Tample and Smith,1996 ; FMC,2003; Yilmaz *et al*.,2004 ; Kol *et al*.,2007 and Wikipedia, 2010) . The same symptom are reported by (Ecobichan,1991 ; Reigarts,1999 and FMC,2003) in addition to salivation , tremors ,paralysis ,respiratory failure and death . While, skeletal and smooth muscle effects including muscular fasculation in limbs are reported by (Tample and Smith,1996) .The gastro-intestinal tract including epigastric pain , anorexia , nausea and vomiting have been reported by (Smith,1996; Tample and Smith,1996).

Inhalation symptoms appear as sneezing ,nasal stiffness ,head ache ,nausea , incoordination , tremors, convulsion , facial swelling (Reigarts,1999).

In sheep , a high dose of CYP may result in teeth grinding, hyperesthesia , excessive salivation , muscular tremors, incoordination, dyspnoea ,opisthonos and death .(Khan *et al*.,2009). The effects on the central nervous system (CNS) and Peripheral nervous system (PNS)

include head shaking , fatigue , listlessness , mild disturbances of consciousness, convulsions and coma may occur (Tample and Smith,1996).

2-7-2-2-Subchronic Toxicity

No data is available about this toxicity except :

1- A twenty one days dermal study in the rabbit when cyp. given at dose levels of control 2 , 20 , or 200 mg /kg /day is applied in 20% weight / weight , the NOEL is 20 mg / kg 1day and the LOEL affect on the liver is 200 mg / kg / day (EPA,1998;Spray,2008).

2- A twenty one days inhalation study in rats , administered by nose only at concentration of 0, 0.01 ,0.05 or 0.25 mg / l based mainly on the body weight decrease . NOEL is 0.01 mg / l (EPA,1998).

2-7-2-3- Chronic Toxicity

CYP has a low chronic toxicity to humans (Ecobichan,1991) . In animals, symptoms include reduces growth in rats and increased liver weight , and reduced weight gain and mild anemia, increased liver weight in mice. In dogs ,the symptoms are loss of appetite ,incoordination , tremors , while in rabbits, CYP causes pathological changes in thymus , liver , adrenal , lungs , and skin (Ray,2007; FMC,2003).Skin irritation , itching ,pricking sensation , local burning sensation , last about two days .(Ecobichan,1991, Chauhan,2006 eHow,2007) .

Chronic oral studies in the beagle dogs which are dosed 0,1,5or 15 mg /kg /day for 52 weeks show low signs basically in the gastro intestinal tract under the effects in 5 mg /kg / day , while the NOEL was in the 1 mg /kg /day .(EPA,1998) .

2-7-2-3- Aggregate Exposure

The dietary exposure (food) tolerance has been established for the residues of CYP in cattle ,goats , horses , and sheep .(EPA,1998; Ray,2007).

2-7-3- Safety

In rats and rabbits there was no evidence of development toxicity at the highest dose of 70 mg / kg / day in rats and 700 mg / kg / day in rabbits . No death ; but decrease body weight was observed in each study .NOEL in maternal was established at 17.5 mg / kg /day in rats and 100 mg / kg / day in rabbits .(EPA,1998).

2-8- Cypermethrin Effects

CYP has many effects on animals and environment so this investigation shows the withdrawal time , the half – life and then the systemic , haematological effects, enzymes alteration and histopathological effects .

2-8-1- Withdrawal Period

There are variations between these periods depending on the CYP concentration and spp. of animals as follows :

Table (2-3) Withdrawal Period in Sheep and Cattle .

Cypermethrin concentration	Animal	Meat
1.25 % w/v	Sheep	7 days
1.5 % w / v	Sheep 10 ml/10kg / b.w.	7 days
2.5 % w / v	Cattle 10 mg / animal	10 days
10 % w / v	Sheep	14 days
8.5 % w / v	Cattle	Slow

According to (Mehhorn *et al*.,2007 **)**

2-8-2- Cypermethrin half – life

2-8-2-1- Cypermethrin Biological half – life

It is vary from animal to another and among investigators, WHO,(1996) shows that the elimination half life in rats is 10 days and in mice 20 – 30 days , while IPCS,(1995) reported that in humans, the elimination of metabolites CYP was complete in 48 hours after the last dosing of 1.5 mg /kg /day ,but it differs in rats where studies have shown over 99% was excreted within hours ; the remaining 1% is stored in the body fat. But the eliminated half – life is 18 days cis isomer .

Tample and Smith ,(1996) explained that the biological (by rout of exposure) elimination half – life following the oral administration of CYP in volunteers was 16.5 ± 5 hours (range 11-27 hours)while it is shorter in the dermal exposure , that is about 13 ± 5 hours (range 8 – 22 hours).

2-8-2-2- Soil and water half –life

It varies between investigators and researchers . Some of them record that the CYP degrads rapidly but not persistently (WHO,1997) . Other investigators and researchers saied that the one more highest in UK in soil and water , so they say the half – life arrange 7 – 12 days in soil and they record that the cyp. exceeds the Environmental Quality Standard (EQS) and Drinking Water standard (DW) (Jin and G.R.B.,1998; PAN,2000).

Dalali *et al*.(2002) report that the CYP undergoes hydrolysis in the soil after 16 weeks and the half – life is 5 days ; but (SEPA and VMD,2006) show that the cyp. remains biologically active in the soil after 133 days .

The half – life is 8 – 16 days in direct sunlight and it is photo stable . In the soil and water, the half – life is as long as 56 and 100 days respectively (Shah *et al.*,2007) .

CYP is stable under acidic or natural conditions (pH 3 -7) but the hydrolysis in strong alkaline media (pH 12 - 13) decomposes above 220 °C . (Ostize and Khan,1994 ; Dalali *et al.*,2002;Crane *et al.*, 2007).

Field data indicate that (in practice) it is stable in air and light .The biological hydrolysis half – life is 63 weeks at pH =7. The rate of degradation depend upon soil type so the half – life in the sandy soil is 2- 4 weeks (Chapman *et al.*,1993 ; FAO,1996;Crane *et al.*,2007).

The half – life in the fertile soil is between 2 - 4 weeks. It degrades in natural water where the typical half – life is about two weeks (Tample and Smith,1996).

Reigart (1999) showed that CYP was relatively stable with a half – life of 8 – 16 days in direct sunlight . In the soil , studies have shown that the half – life is as long as 100 days . In case of home treatment, CYP persists for about 3 months .(Reigart, 1999).

2-8-3- Toxic Effects of Cypermethrin

2-8-3-1- Hematological and Biochemical Effects

Rabbits with a sublethal dose of CYP 124 mg /kg bw have a significant increase in plasma total lipids (TL) , cholesterol , triglyceride (TG) levels , low density of lipoprotein (LDL) , very low density of lipoprotein (VLDL) , glucose , urea , creatinine , and total bilirubin , while there is decrease in the high density lipoprotein (HDL) , total protein (TP) , albumin (A) , while globulin (G) and A / G ratios are not significant (Yousef, *et al.*,1998 ;Khan *et al*.2003; Yousef *et al*.2003) .

Blood shows a decrease in Hb% , Total Erythrocyte Count (TEC) ,PCV , while Total Leukocyte Count (TLC) increase (Yousef *et al*.2003) ,but (Roberts,1987) finds no significant increase TP . No effects has been reported on Hb concentration in rats by other investigators (Mansee,1998; [a]Ahmad *et al*.,2009) .

Studies on sheep have reported significant decreases in Hb , TEC , PCV , and MCHC with increase MCV in goats treated with CYP (Tample and Smith,1996 ;Yousef, *et al*.,1998; Samita *et al*.,1999; Khan,2005; [a]Ahmad *et al*.,2009;Khan *et al*.,2009) .

There are also significant decreases in AST, ALT , ALP in sheep treated with CYP (Yousef, *et al*.,1998) , but the ER cholinesterase levels and plasma cholinesterase were inhibited in sheep treated with CYP (Yousef, *et al*.,1998 ; Khan *et al*.,2003).

However , ([a]Ahmad *et al*.,2009) report significant increase in Hb% , TEC , PCV in mice. Anemia may or may not induced in rabbits treated with CYP .

2-8-3-2- Immunological effects

CYP induces a humoral immune response in rabbits against *S. typhi* following the administration of CYP .The cell - mediated immune response decreases (Desi *et al*.1986; EMEA,1998,2003,2004;Liu *et al*.,2006). CYP also interfere with the tuberculin skin test.(Cox,1996).

2-8-3-3-Reproductive Effects

No adverse effects on reproduction are observed in a three generation study with rats given CYP at doses of 37.5 mg /kg /day (He *et al*.,1989; Hayes and Laws,1990).

As teratogenic effects, in pregnant rabbits, CYP can affects the offspring in relation to the number of organs and skeletal abnormalities while in rats, it delaied such events as tooth emergence , eye opening , and in mice, it increases the abnormal sperms .(He *et al*.,1989;Chapman *et al*.,1993).

One study involving 30 males of dwarf goats is conducted to determine the effects of CYP on semen characteristics and concentrations. The effects which found includes : a decrease in the ejaculatory volume , motility percentage , mass activity , alkaline PH , color change from creamy to milky–straw color and increase the percentage of the spermatozoa abnormalities and death **(**[b]Ahmad *et al*.2009 **).**

2-8-3-4- Mutagenicity and Carcinogenicity

CYP was found to be genotoxic in the mouse spleen and bone marrow but other studies have been negative. EPA has classified CYP as possible human carcinogen . (He *et.al*.,1989 ; Hayes and Laws,1990 ;Chapman *et.al*.,1993).

2-8-3-5-Soil Microbial Effects

There is a response of soil microbial communities to the addition of CYP . Gram negative bacterium identified as *Pseudomonas putida* effectively removed 75 % of CYP from a medium at 30 °C with 28 days .(Canon,2008).

CYP removal is shown to be microbially mediated. Approximately 50 % of CYP was removed from soil amended with 100 mg / kg-1 after 56 days ,with most degradation occurring within the first 3 days(Canon,2008) .

No significant CYP removal is observed in the soil amended with 1000 mg / kg -1 CYP **.** Cypermethrin does not actually have adverse effects on the soil microbial nor does it inhibit the growth of some common soil bacteria . The fungal community composition was strongly influenced by CYP (Canon,2008) .

2-9- Residues of Cypermethrin in Ruminant Tissues

Ruminant species such as bovine , ovine , caprine show a similar gastro – intestinal physiology . The available pharmacokinetics and residues depletion data do not indicate any significant variability between cattle , sheep and goats , therefore ;it is considered that other ruminants are unlikely to show any significant differences in these parameters .(EMEA,1998,2003,2004).

The existing tissue maximum residue limits (MRLs) for bovine and ovine species are identical and so it is considered appropriate to recommende the extension of the MRLs so that the same tissue MRL values would apply to all ruminants .The MRL for bovine milk is also recommended to be extended to all ruminants (EMEA,1998,2003,2004) . But there is wide variety of MRLs according searchers as follows : Some investigators reported the MRLs for cattle and sheep are 200 µg / kg in the muscles , liver , and kidney ,and 100 µg / kg in fat , 50 µg / kg for cattle whole milk (Beyerbach,2000 ; FAO/WHO,2002) . While(PMEP,1989) a pointed to fat and milk residues in cattle , goats and sheep which were 0.05 mg / kg ,but (EMEA,1998,2003,2004) reported that the MRLs in bovine and ovine tissues were as follow : Muscles hade 20 µg / kg , fat 200 µg / kg ,and 20 µg / kg were found in liver and kidney . Bovine milk residues were 20 µg / kg .

2-9-1- Residues in Sheep

2-9-1-1-Oral Dosing

Three groups of 5 adult sheep of both sexes are given oral dose of 1mg / kg b.w of CYP , then are slaughtered at 1 , 3 , and 5 days after dosing ,it is found that the main values of total residues are three times more in liver than kidney and approximately 1.3 time higher than in fat at 5 days . (Beyerbach,2000 ; FAO/WHO,2002).

But in other study, 2 sheep are orally dosed with 1 mg / kg b.w ,then sheep are killed 7 days after treatment .The percentages of residues are 4.1 , 22 , and 86 % of the total residue in the liver , kidney , muscle and fat respectively .(Smith *et.al*,1996 ; EMEA,1998,2003,2004).

In the same study ,sheep are orally dosed with 1 mg / kg bw of cyp. then 5 animals are killed at 1 , 2 , 3 , days after dosing .The main residues in the liver are 334 , 135 and 66 µg / kg while in fat 50 , 73 , 52 µg / kg and in muscles, the residues are 13 , 8 , 5 , µg / kg at the same periods of study . (EMEA,1998,2003,2004).

2-9-1-2- Topically Treated

In this subject , the results of some investigators and researchers are shown as the follows :

Two male sheep were topically treated with CYP at dose of 21.9 mg / kg bw , while a third group is orally dosed by 3.9 mg / kg b w .The residues are measured. A higher concentration is observed in fat compared to muscles and organs tissues .

The results are shown in Table (2-4) (in %).

Table(2-4): Residues of CYP After Topical Treatment in Sheep(in %)

Tissue	Topical 24 hours	Topical 6 days	Oral 2 days
Liver	13	17	18
Kidney	< 3	< 4	< 1
Muscle (shoulder)	* nq	* nq	33
Fat (renal)	88	80	63
Fat (subcutaneous)	-	92	67

*** nq : not quantifiable .**

According to (Roberts , 1987 ; Beyerbach,2000 ; Adriana,2004)

And the values of these residues are shown below by µg / kg .

Table (2-5) : Residues of CYP After Topical Treatment in Sheep by µg / kg

Route of administration	Time post dose	Muscle	Liver	Kidney	Renal fat	Sub. fat
Topical	1	30 – 40	100	140	170	100000 *
Topical	6	30 – 60	140	120	300	3300 *
Oral	2	30 – 40	390	360	410	260

* At the site of applied .

This table reported according to (Roberts , 1987 ; Beyerbach,2000 ; Adriana,2004).

Sheep after dipping the residues in ewe's milk after one dipping with 0.015 % formulation of CYP It is found that the residues persisted

throughout 15 days post dipping .The main values in µg / kg at 1 , 3 , 7 ,10 , and 15 days are 13 , 10 , 9 , 7 , and 7 respectively . When the milk carries about 5.8 % of fat , the residues measured in the fat are 206 µg / kg on day 7 which represents the highest concentration (Beyerbach,2000).

In the pour – on studies on 20 sheep treated with 0.375 g and 20 sheep treated with 0.75 mg of CYP the residues reach 40 µg / kg at 3 – 7 days after treatment . These values decrease to 20 µg / kg at 28 days after treatment in both perirenal and omintal fat (WHO,1996 ; Beyerbach ,2000).

In another study ,10 sheep were treated with 0.375 g of CYP in two different pour – on formulations .The residues at 7 days post treatment are 18 – 25 µg / kg in the omental fat and 4 – 10 µg / kg in the perirenale fat . (Beyerbach,2000;FAO/WHO,2002**) .**

Twenty four sheep are treated by CYP as dipping by 0.01 %,the residues were detected in omintal fat , perirenal fat and muscle at a level ranging from < 10 µg / kg at 0 day and up to 170 µg / kg in perirenal fat at day 14 . (WHO,1996; Beyerbach,2000).

2-9-2 - Residues in Goats

In another study on goats were treated topically with a commercial pour –on formulation at the dose rate of 4 mg / kg b.w of CYP . The residues at the following : the mean residues in the kidney fat were 7 µg / kg at the 7 day while they are 140 µg / kg at 14 days and 10 µg / kg at the 42 days after treatment . In another study , lactating goats were treated with the same dose of pour – on (4 mg / kg b.w) the residues in milk are 20 µg / kg at 24 hours after treatment , 25 µg / kg at 32 hours and below 10 µg / kg at 96 hours after treatment (EMEA,1998,2003,2004).

2-9-2- Residues in Cattle

A diet containing 10 mg / kg of CYP for cattle the results of residues in milk is 90% of both cis and trans isomers . In fat that is removed by a solvent extraction 98 % . In addition, 90 % of the fat residue is shown to be the parent CYP. In muscle < 10 µg / kg so it is in kidney (Roberts,1987) .

Another study shows cattle residues of cyp. in oral dosed cattle that are slaughtered on the last day of the dosing :

Table (2-6):Cattle Residues of CYP in Oral Dose .

Dose mg / kg feed	Milk	Muscle	Liver	Kidney	Renal fat	Subcutaneous fat
0.2	1.2	< 1	4.8	3.4	10.12	8.9
5	13.1	< 40	100	50 – 130	30 -100	10 -60
10	31	10	210	110	100	80

According to (Beyerbach,2000)

These values were measured by µg / kg except for milk which is measured by µg / l (Beyerbach,2000).

In lactating cows administred twice daily with CYP in the doses 0.2 , 5 and 10 mg per kg of food , the residues in tissues measured after 7 , 20 , and 21 days of treatment are low and in the following order : liver > kidney > renal fat > subcutaneous fat > blood > muscles > brain . Then residues are measure in the liver and kidney of cows that received 10 mg / kg of diet . (Woolen *et.al*.,1992; Chen *et.al*.,1997).

Calves are treated topically with a pour – on formulation at approximately 41 mg / kg b.w and then killed in groups of 5 animals at 3 , 7 , 14 days after treatment . the liver residue is 10 µg / kg in all groups

, while in the muscles it is detected only in the day 3 .Samples mean residue is 24 µg / kg , while in kidney the residues are 66 µg / kg at the 7th day and 40 µg / kg at the 14th days of treatment . Residues are the highest in fat :the mean residues are 260 µg / kg and 670 µg / kg and they are found in the subcutaneous and perirenal fat respectively at the 7th days after treatment . while, at 14th days, they are 140 and 330 µg / kg . (Chen *et.al*.,1997;EMEA,1998,2003,2004).

In lactating cows treated topically with pour – on CYP at a dose of 1.25 mg / kg b w residues are 25 µg / kg in the milk at 24 hours after treatment ,48 µg / kg at 48 hours after treatment and 7 µg / kg at 7 days after treatment . (Chen *et al*.,1997;EMEA,1998,2003,2004)

When cows are treated topically with 2.5 mg / kg bw of cyp. the mean residues in milk at the 3 time – points are 63 µg / kg , 99 µg / kg and 13 µg / kg respectively (Chen *et.al*.,1997;EMEA,1998,2003,2004).

2-10- Treatment and Management

In humans, there is no anti dote .(Flannigan *et al.*1985), but the management is done by : avoiding administration of milk , cream , or other products which contain vegetable or animals fat as they enhance absorption .CNS stimulation should be controlled with sedation , for example barbiturates . A reversible skin sensation (paresthesia) may occur and ordinary salves have been found useful in reducing discomfort . (FMC,2003). But remember the treatment is essentially symptomatic and prevent further absorption .(Flannigan *et al*.1985).

When bronchospasm or anaphylaxis occurs, convulsions are controlled by appropriate drugs regimen .Eye contamination is treated by copious water or saline immediately for long time .(Flannigan *et al.*1985 ; Chapman *et al*.,1993 **).**

Chapter Three

Materials and method

3- 1- Experimental Animals and Managements

Twelve local sheep of both sexes , age range between eight to fourteen months and body weight about 29 to 35 k g .All sheep taken from the animals field of veterinary college in Basrah university . This animals was divided randomly into three equal groups .

The first group served as the control group (C) and the second served as the treated group (T) for the chronic experiment, while the third group used for acute experiment . All animals were kept under the same conditions of managements and feeding , it was conducted according to the local breeding conditions .The animals were treated with Albendazole and Oxytetracyclin then acclimatized for 15 days before starting the experiment .

3-2- Instruments

No.	Name	Origin or Company
1	Stethoscope	China
2	Thermometer	China
3	Microhaematocenterifuge	Kirkuk
4	Macrocenterfuge	Brazil
5	Microscope	China
6	Incubator	Biwder , model 301 / Germany
7	Spectrophotometer	Pd – 303 Aple company / Japan
8	Haematocytometer	Marifeld / Germany
9	Camera	Kudak / Korea
10	Syringes in different sizes	China

11	Haematocytometer slide	Germany
12	Test tubes (with and without anticoagulant)	China
13	Post mortem equipments	China
14	Plastic containers for histopathological sample	China

3-3- Chemicals

No.	Name	Origin or company
1	Giemza stain	India
2	HCl 10 %	Jordon
3	Normal saline	Egypt
4	Sodium hydroxide 0.4 m /m	Germany
5	Haymes solution	Egypt
6	Cypermethrin (® Cypervite)	KSA
7	Buffered formalin 10 %	Syria
8	**Commercially available kits :**	
a	Urea / BUN – liquienzyme	Spectrum company / Egypt
b	Creatinine – kinetic method	Biolabo / France
c	(ALP) Alkaline phosphatase –	Spectrum company / Egypt
d	color metric kit	
e	Alanine aminotransferase (ALT /	Spectrum company / Egypt
f	GPT)	
g	AST / TGO – color metric	Biolabo / France
	method	
	LDH(SFBC) kinetic method	Biomagreb
	Total protein	Spectrum company / Egypt

3-4 - Experimental Design

3-4-1- Chronic Experimental Design

The first group was given orally CYP 0,1% with tab water at dose of 17 mg / kg b.w daily for 63 days , while the second group served as control group and administered with drinking water only .

3-4-1-1- Samples Test and Clinical Signs

a – Clinical Signs

Animals were observed twice daily for the onset of clinical toxic signs (toxication effects of CYP) and changes in vital signs (temperatures, respiratory and pulse rate) were recorded .

b - Blood Samples

Blood samples were collected at pre exposure and 15 , 30 , 45 and 63 days after treatment and divided into two portions ; the first portion was kept with anticoagulants and used for haematological examinations ,while the other kept without anticoagulants and used for the serum extraction which frozen until use for biochemical tests.

c – Hematological Examinations

It was done immediately after samples collection and it include red blood cells count (RBC) , hemoglobin concentration (Hb%), packed cell volume (PCV) according to.(Coles;1986)

Erythrocytes indices including means corpuscular volume (MCV) , means corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) were calculated according to equations described by Coles (1986) .

d - Biochemical Examinations

Biochemical tests include Alanine aminotransferase (ALT) , Aspartete aminotransferase (AST) , Alkalin phosphatase (ALP) , lactate dehydrogenase (LDH) , blood urea nitrogen (BUN) , creatinine (Cr.) and total protein (TP) .They were measured by using available commercial kits according to it's procedures .

3-4-1-2- Gross and Histopathological Studies

At the end of experiment at the 63 days later, the animals of the treated group were slaughtered . Each carcass was examined alone and samples of each tissue lesion was collected and fixed in 10 % buffered formalin immediately .

Histopathological procedures was prepared by histopathological unit in Al-Sadr medical teaching city in Al-Najaf then slides were tested for histopathological changes by specialists in pathological department of veterinary college of Basrah university .The eosin and hematoxylin stains were used for staining all the prepared sections .

3-4-2- Acute Experimental Design

In this experiments the third group of sheep of both sexes was treated orally with CYP at a dose of 70 mg / kg b.w as a single dose .

Clinical signs were observed at zero time, 6, 12 ,24 hours of the dosing . Serum and blood samples were drawn at the periods above ; the hematological and biochemical studies has been made immediately at zero time , 6 , 12 , 24 hours of dosing according to (Coles ; 1986) .and the commercial kits respectively .While the gross lesions and histopathological samples was conducted after animals slaughtered (after 24 hours) , these examinations and tests were done similarly to those of the chronic experiment oral administration with cypermethrin .

Chapter Four

Results

4- Results

4-1- Chronic Experiment (Cypermethrin dose:17 mg / kg b.w.)

4-1-1- Clinical Signs :

After 15 minutes of dosing, the animals show signs of head shaking which continues for 40 – 60 minuets of the 3 – 5 days after daily administration ; then the animals show no signs after the 5 days of the first dosing .

A bad odor of faeces appears at the 2nd days of administration; which become diarrhea at the 5th days of dosing with yellow – greyish color .The diarrhoea was stopped in two animals of the treated group at the 36th days of the first dosing , but in the other two animals the diarrhoea stopped at 45th days of experiments .

Lips licking appears immediately after dosing and persist for the 3rd day of the daily administration .

Dullness , inappitance , raised head up ward as high as possible . Pica appear at 18 – 19 days of the first dosing and it was represented by wall and objects liking and wool eating , wool was easy removed .

The frequency of urination increased at the 2nd day .

Dietary consumption increase and tend to green food at the 3rd week of dosing , but the pica and this symptom persist to the end of the experiment .

4-1-2- Temperatures

The means of temperatures in the treated and control groups were illustrated in table (4-1) . There was no significant difference in the mean of temperatures between the two groups throughout the study .

Table (4 – 1) :- Means of Temperature of Sheep Treated with CYP

Week	Treated group Mean ± Standard error	Control group Mean ± Standard error	P.Value
1	39.3 ± 0.03	39.35 ± 0.025	p > 0.05
2	39.45 ± 0.042	39.43 ± 0.032	p > 0.05
3	39.47 ± 0.031	39.40 ± 0.025	p > 0.05
4	39.52 ± 0.032	39.55 ± 0.21	p > 0.05
5	39.62 ± 0.09	39.59 ± 0.082	p > 0.05
6	39.58 ± 0.075	39.61 ± 0.12	p > 0.05
7	39.63 ± 0.071	39.62 ± 0.082	p > 0.05
8	39.43 ± 0.062	39.45 ± 0.062	p > 0.05
9	39.56 ± 0.095	39.59 ± 0.061	p > 0.05

4-1-3- Pulse Rate

The means of pulse rate were illustrated in table (4-2) . The pulse rates were increased significantly ($p<0.05$) in the T group during the 5 - 7 weeks and continue increasing ($P<0.01$) from the 8^{th} week until the end of the experiment .

4-1-4- Respiratory Rate

Respiratory rate were showed significant increase ($p<0.05$) in the T group at the beginning of the 5^{th} week after oral administration and this result persisted until the end of experiment .The mean of the respiratory rates were illustrated in table (4 - 3) .

4-1-5- Haematological Parameters

There is a significantly decreased in the RBC count, Hb % and PCV ($p<0.05$) in the T group during the 30 days of the first dosing and similar results were reported until the end of the experiment as shown in tables (4-4 , 4-5 and 4-6) respectively .

Table (4 -2) : Means of Pulse Rate of Sheep Treated with CYP.

Week	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
1	89.5 ± 4.5	85.46 ± 3.23	P > 0.05
2	87.0 ± 4.6	82.03 ± 3.3	P > 0.05
3	89.03 ± 1.94	86.5 ± 2.1	P > 0.05
4	86.95 ± 2.7	88.89 ± 2.86	P > 0.05
5	100.46 ± 2.52	85.10 ± 2.59	P < 0.05
6	102.28 ± 2.38	83.75 ± 3.18	P < 0.05
7	106.7 ± 1.91	85.2 ± 3.06	P < 0.05
8	109.5 ± 2.56	82.96 ± 3.2	P < 0.01
9	115.46 ± 3.37	84.32 ± 4.8	P < 0.01

Table (4 –3) :Means of Respiratory Rate of Sheep Treated with CYP.

Week	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
1	26.2 ± 0.31	25.1 ± 0.32	P > 0.05
2	25.2 ± 0.25	26.3 ± 0.53	P > 0.05
3	28.3 ± 0.62	28.4 ± 0.31	P > 0.05
4	28.4 ± 0.34	28.7 ± 0.52	P > 0.05
5	36.2 ± 0.9	26.25 ± 1.3	P < 0.05
6	45.5 ± 1.5	28.32 ± 1.2	P < 0.01
7	52.3 ± 2.2	28.62 ± 1.5	P < 0.01
8	60.3 ± 1.2	27.96 ± 1.4	P < 0.01
9	64.5 ± 0.92	28.12 ± 1.3	P < 0.01

Table (4 - 4) : Means of PCV % of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	30.25 ± 1.08	31.75 ± 2.6	P > 0.05
15	31.25 ± 2.83	30.50 ± 2.78	P > 0.05
30	25.5 ± 1.65	32.75 ± 2.7	P < 0.05
45	22.25 ± 0.85	33.75 ± 2.85	P < 0.01
63	19.75 ± 0.94	33.75 ± 2.48	P < 0.01

Table (4 - 5) : Means of Hb g / dL of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	9.5 ± 0.4	9.25 ± 0.32	P > 0.05
15	9.75 ± 0.25	9.5 ± 0.36	P > 0.05
30	7.25 ± 0.36	9.0 ± 0.2	P < 0.05
45	7.0 ± 0.23	9.75 ± 0.43	P < 0.01
63	6.25 ± 0.51	9.5 ± 0.20	P < 0.01

Table (4 – 6) : RBCs by X 10^{12} cell / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	8.25 ± 0.12	8.31 ± 0.16	P > 0.05
15	8.35 ± 0.25	8.36 ± 0.26	P > 0.05
30	5.23 ± 0.33	8.25 ± 0.37	P < 0.01
45	4.22 ± 0.21	8.32 ± 0.82	P < 0.01
63	3.48 ± 0.28	8.26 ± 0.63	P < 0.01

Comparatively there is no significant difference in the means of MCV and MCHC between the T and C groups in the experiments .

The means of MCV and MCHC are illustrated in tables (4-7 and 4-8) respectively .

Table (4 – 7) : Means of MCV fL of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	24.6 ± 0.6	24.4 ± 0.5	p > 0.05
15	24.1 ± 0.55	24.2 ± 0.62	p > 0.05
30	24.7 ± 0.65	24.8 ± 0.75	p > 0.05
45	24.9 ± 0.32	25.6 ± 0.83	p > 0.05
63	25.4 ± 0.62	25.3 ± 0.95	p > 0.05

Table (4 – 8) :Means of MCHC g / dL of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	36.67 ± 1.9	36.2 ± 0.95	p > 0.05
15	36.22 ± 1.7	36.12 ± 1.2	p > 0.05
30	36.43 ± 1.3	36.52 ± 1.5	p > 0.05
45	36.51 ± 2.3	36.6 ± 1.4	p > 0.05
63	36.35 ± 3.5	36.37 ± 1.3	> 0.05

4-1-6- Biochemical Results

4-1-6-1- Liver Enzymes

In the biochemical studies, there were significant increases in the liver enzymes : LDH , AST , ALT and ALP ($p<0.01$) in the T group during the 30 days of the first inoculation and similar results were reported in the following days until the end of the experiment ,these values of liver enzymes were illustrated in tables (4-9 , 4-10 , 4-11 and 4-12) respectively .

Table (4 – 9) : Means of LDH IU / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	146.25 ± 6.86	152.25 ± 5.55	p > 0.05
15	156.75 ± 5.93	161.5 ± 11.93	p > 0.05
30	192.5 ± 8.3	163.75 ± 7.3	P < 0.01
45	423.0 ± 9.3	165.25 ± 8.1	P < 0.01
63	522.5 ± 11.2	153.5 ± 6.2	P < 0.01

Table (4 -10) : Means of AST IU / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	45.25 ± 2.08	48.42 ± 2.1	p > 0.01
15	46.5 ± 2.62	45.25 ± 2.3	p > 0.01
30	65.5 ± 3.3	46.5 ± 3.1	P < 0.01
45	78.75 ± 3.5	48.75 ± 2.4	P < 0.01
63	110.5 ± 4.2	48.25 ± 1.9	P < 0.01

Table (4 -11) : Means of ALT IU / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	25. 5 ± 1.9	23.5 ± 1.4	p > 0.05
15	26.75 ± 2.5	27.25 ± 1.8	p > 0.05
30	35.25 ± 2.8	26.75 ± 2.3	P < 0.01
45	46. 5 ± 2.5	27.25 ± 2.3	P < 0.01
63	65.0 ± 2.9	27.75 ± 1.5	P < 0.01

Table (4 -12) : Means of ALP IU / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	162.25 ± 1.9	164.25 ± 1.7	p > 0.05
15	166.5 ± 2.5	167.25 ± 2.8	p > 0.05
30	195.5 ± 4.3	170.5 ± 3.5	P < 0.01
45	223.75 ± 4.5	172.5 ± 3.2	P < 0.01
63	265.5 ± 4.2	171.25 ± 4.3	P < 0.01

4-1-6-2- Total Protein

The total protein was showed significant decrease (p<0.01) in the T group during the 15 days of the first dosing with CYP. and this decreased persist until the end of experiments . Table (4-13) explain this result .

Table (4 -13) : Means of TP g / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	64.2 ± 2.6	66.8 ± 1.8	p > 0.05
15	39.2 ± 1.77	64.3 ± 2.2	P < 0.01
30	36.2 ± 1.32	65.5 ± 1.3	P < 0.01
45	32.4 ± 2.16	66.3 ± 2.4	P < 0.01
63	23.7 ± 0.44	63.9 ± 2.8	P < 0.01

4-1-6-3- Kidney Function Tests

Blood urea nitrogen and Creatinine show significant increases in the T group during the 30 days of the first dosing and the similar result were reported until the end of experiment .These results were listed in tables (4-14 and 4-15) respectively

Table (4-14) : Means of BUN mmol / L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	2.25 ± 0.21	2.85 ± 0.25	p > 0.05
15	2.82 ±0.3	2.84 ± 0.27	p > 0.05
30	4.62 ± 0.51	2.93 ± 0.35	P < 0.05
45	8.25 ± 0.62	2.95 ± 0.32	P < 0.01
63	12.62 ± 4.2	2.92 ± 0.41	P < 0.01

Table(4-15):Means of Creatinine µmol/L of Sheep Treated with CYP.

Day	Treated group Mean ± Standard error	Control group Mean ± Standard error	P. Value
Zero Time	96.3 ± 5.3	95.2 ± 5.4	p > 0.05
15	98.5 ±5.6	99.3 ± 4.3	p > 0.05
30	122.3 ± 4.5	98.2 ± 3.5	P < 0.01
45	167.5 ± 4.9	100.3 ± 3.7	P < 0.01
63	174.25 ± 4.2	99.5 ± 3.2	P < 0.01

4-1-7- Gross and Histopathological Changes

4-1-7-1- Gross Lesions

After animals killing at the 63 days of the experiments , post mortem examination was done and the gross lesions which reported included: Congestion of subcutaneous blood vessels , intestine , kidney and spleen which appear as dark black in color , liver , thoracic cavity blood vessels mesenteric blood vessels , lungs with grey hepatization , brain and trachea .There was an enlargement of mesenteric lymph nodes , kidneys and gall bladder which contain dark serous fluids .When cross section was done to the spleen , liver and lungs, there were observed of ooze blood from the cut sites ,gaseous dilatation of intestine . Figures (1 and 2) show some of these gross lesions .

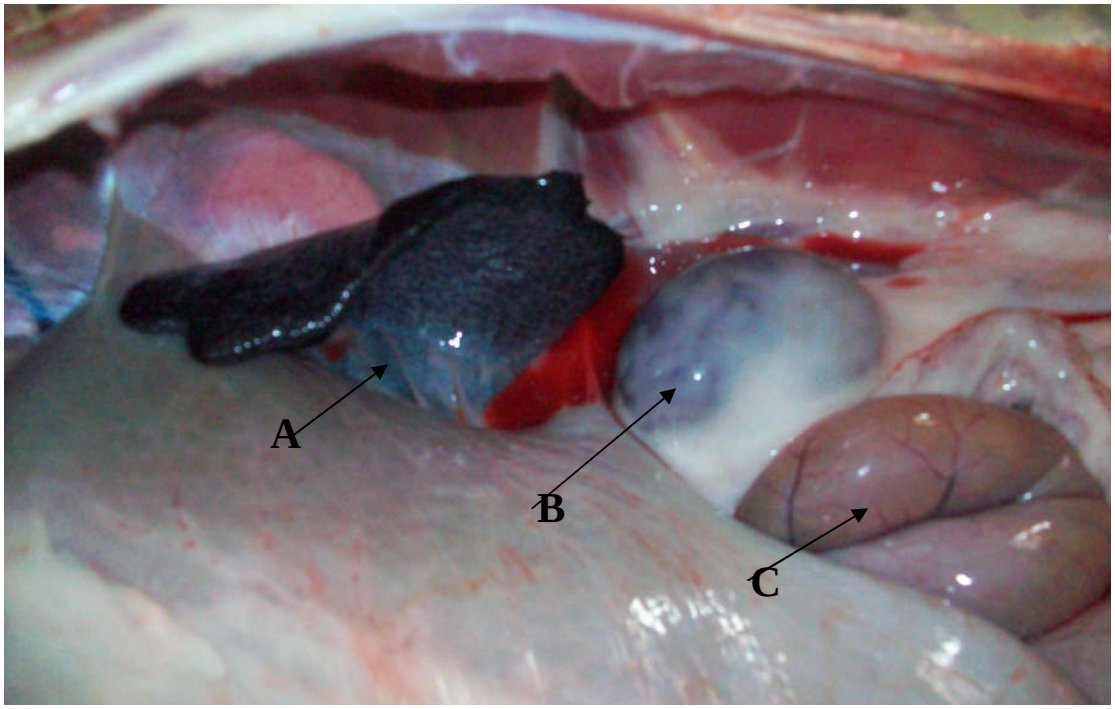


Fig.(1) A) Spleen: appear as dark black in color B)Kidney: enlargement. C) Intestine :congestion and gaseous dilatation.

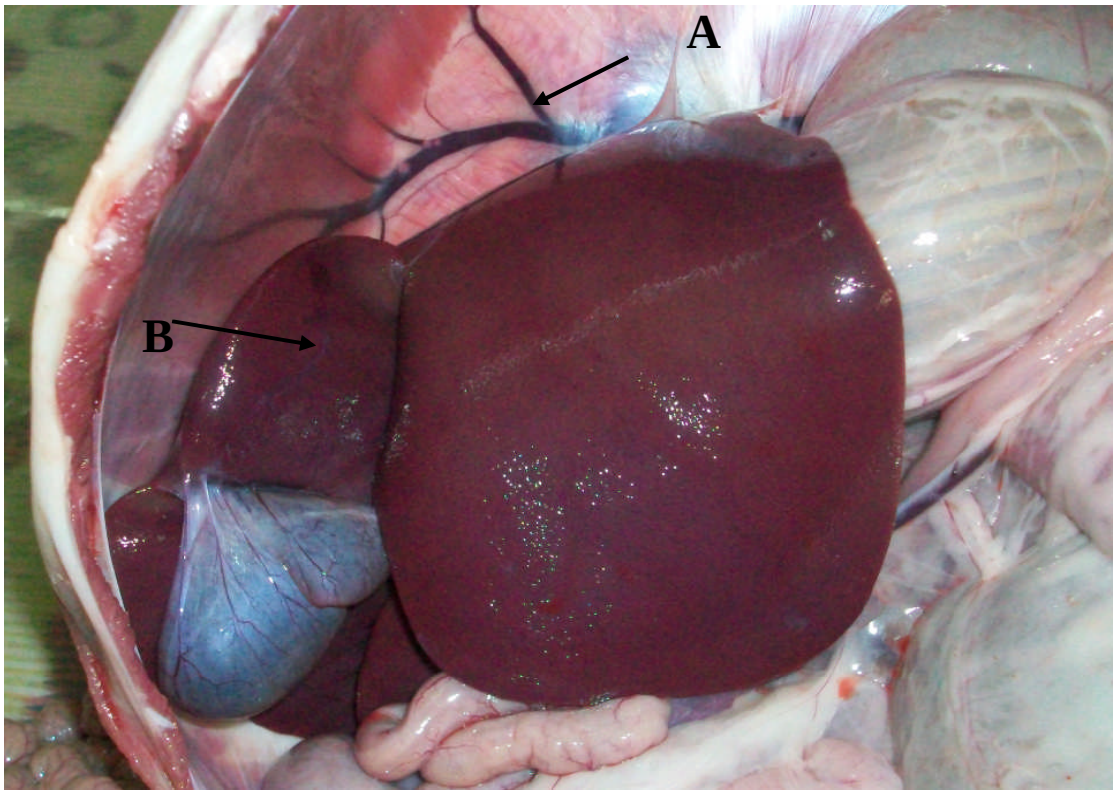


Fig.(2) Congestion of: A) thoracic cavity blood vessels B) Liver .

4-1-7-2- Histopathological Changes

After the histopathological examinations were done ,the results were reported according to the organs as the following :

1-Nervous Tissues

In the brain (cerebellum) there was a vacuolation of neurons in the gray mater of cerebellum ,and the medulla oblongata appear vacuolation of nerve fibers . figure (3 and 5) .In the spinal cord there was vacuolations of medulla ,but the peripheral nerves (Ischiatic nerve) have occasional vacuolation of nerve fibers , figure (4) .

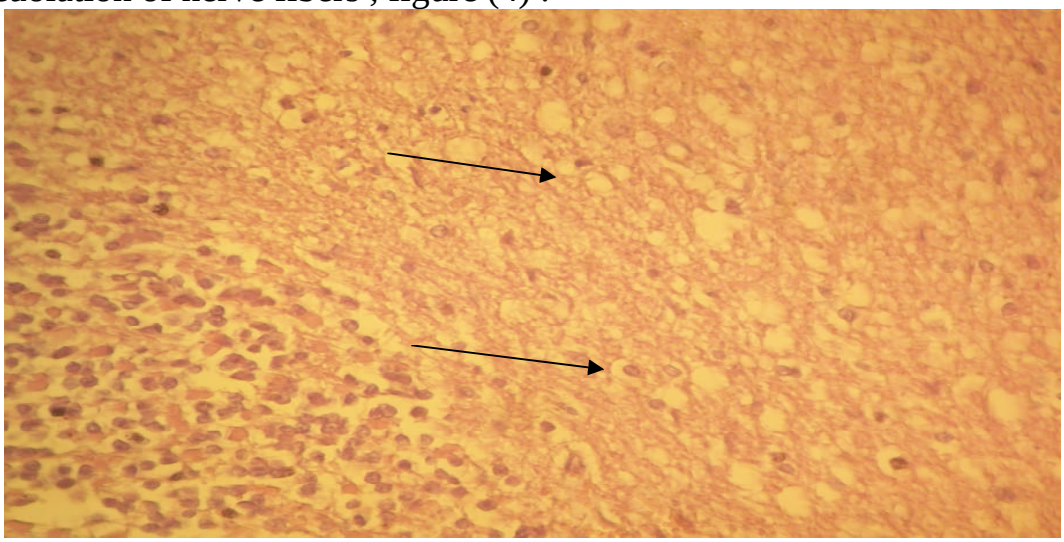


Fig.(3) Brain cerebellum : vacuolated nerve fibers of the white matter.400X (H. and E. Stain)

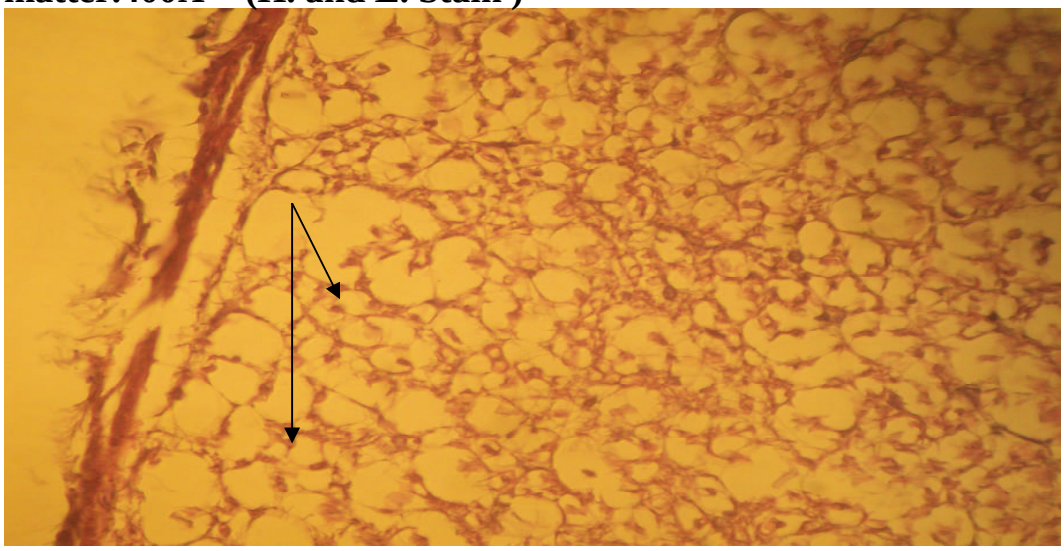


Fig. (4) spinal cord (thoracic): sever vacuolation in the nerve fibers in the white matter.400 X (H. and E. Stain)

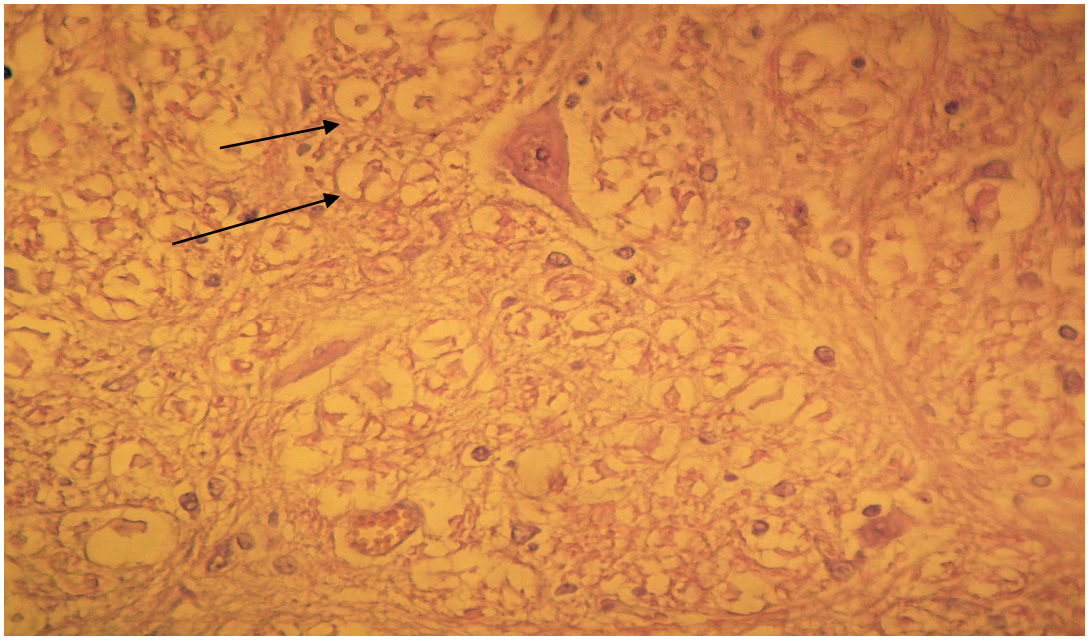


Fig.(5) Medulla oblongata : vacuolation of nerve fibers in the white matter . 400X (H. and E. Stain)

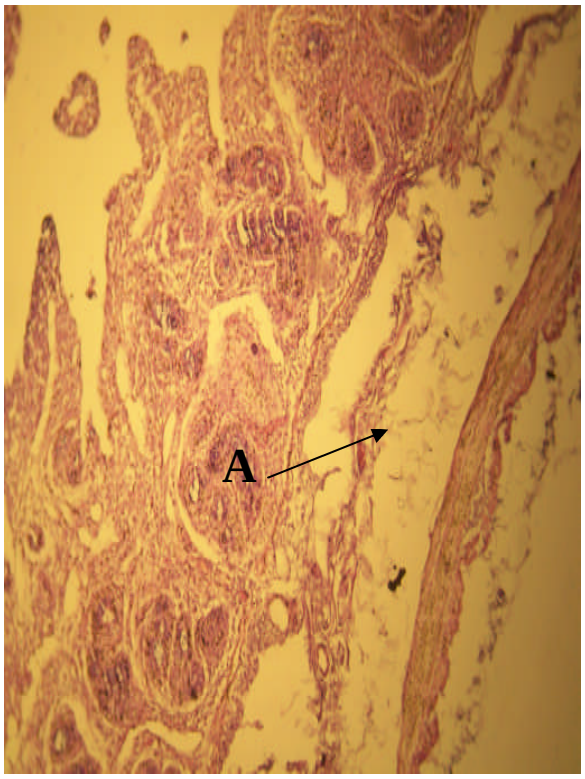
2-Gastro-entestinal Tract

In the abomasum, there was an edema and vacuolation of the submucosal epithelium which was probably associated with an increase of mucosal secretions and proliferation of mucous glands . figures (6 and 7) .

Rumen has probably projections of the lamina propria and congestion of small blood vessels as well as vacuolation of the top of rumen lamina propria . figure (8) .

3 - Liver

The liver was show a minimal or slit fibrosis of the peripheral region with congestion of the hepatic vein . figure (9).



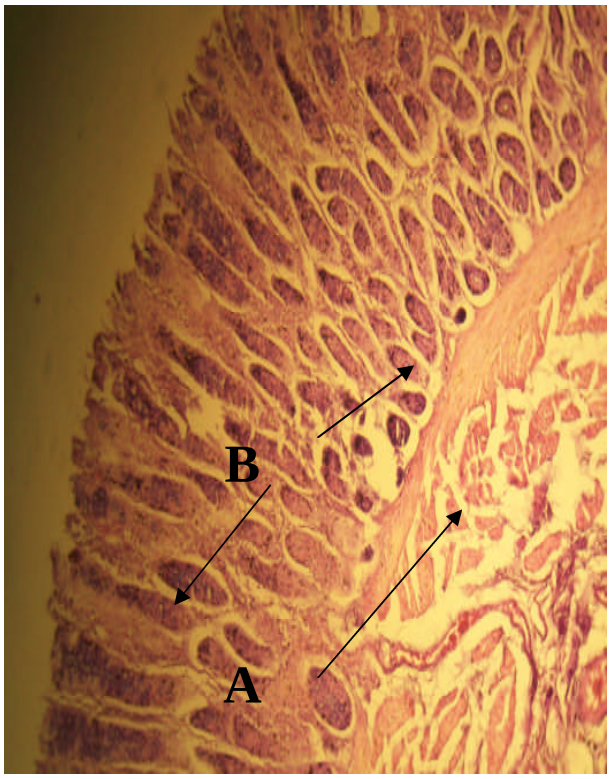


Fig.(6)Abomasum: 400 X

Fig.(7)Abomasum: 100 X

(A) edema of submucosa (arrow) , (B) proliferation of mucous glands (H. and E. Stain)

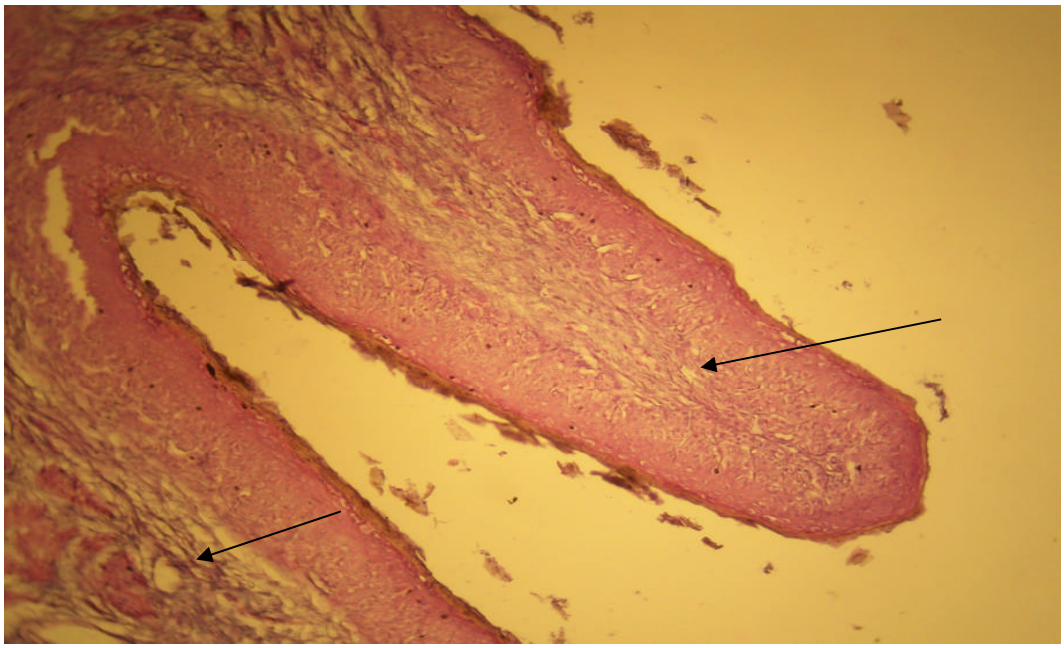


Fig.(8) Rumen : vacuolation of the top of rumen lamina propria . 100 X (H. and E. Stain)

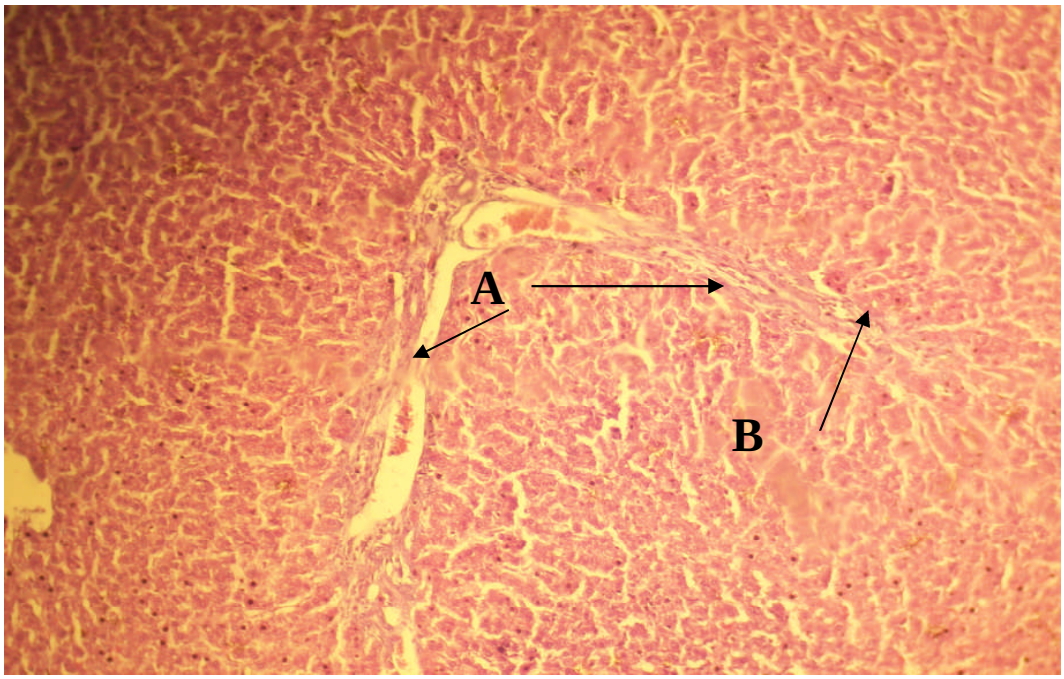


Fig.(9) liver (A) minimal fibrosis of the peripheral region (arrows) (B) congestion of hepatic vein (arrow) .100X (H. and E. Stain)

4- Testis

There was a suppression of spermatogenesis with no evidence of the presence of spermatozoa in the lumen and there was a vacuolation of spermatogonia . figure (10).

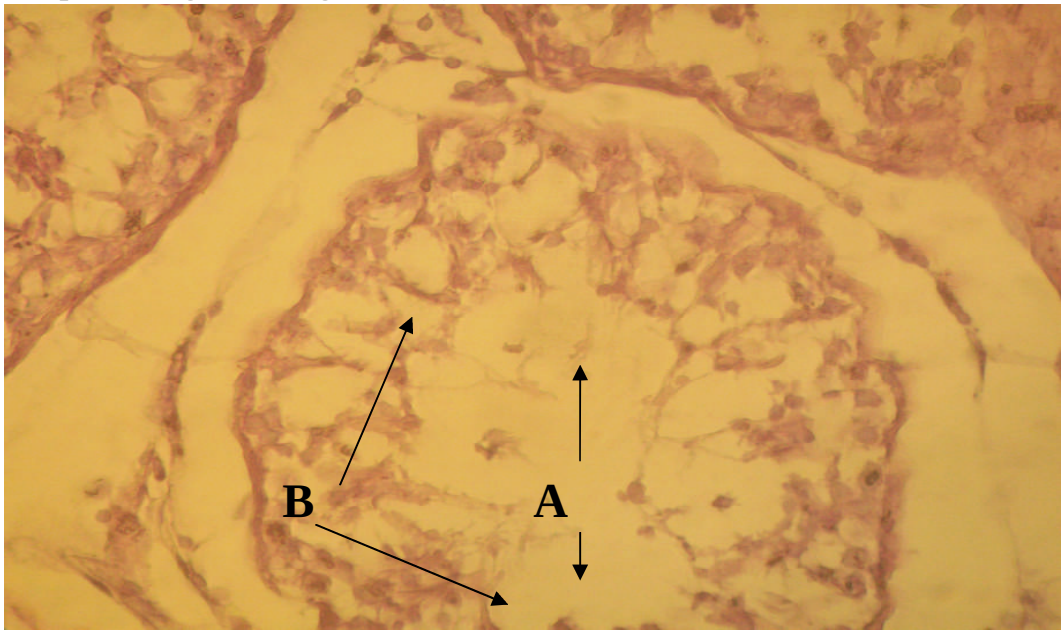


Fig.(10) Seminiferous tubule : (A) suppression of spermatogenesis (arrow) (B) Depletation of spermatogonia (arrow) . 400 X (H. and E. Stain)

5- Heart

Only the vacuolations of myocardial muscles cells have been reported in the heart . Figure (11) .

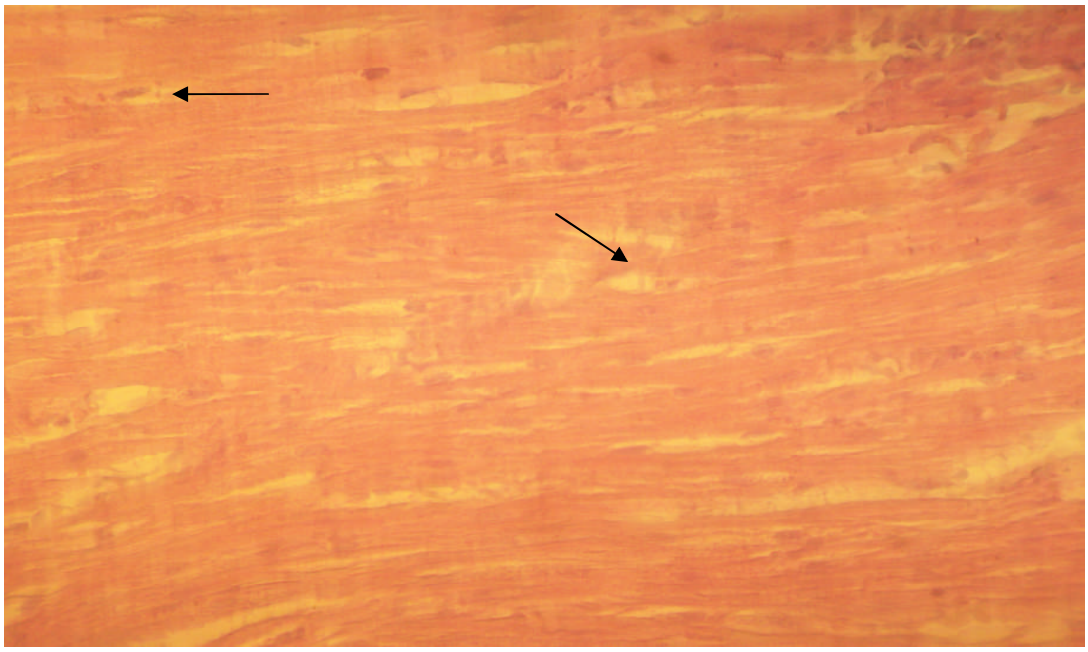


Fig.(11) Heart : vacuolations of myocardial muscles cells 400X (H. and E. Stain)

6- Bone marrow

There was a prominent adipose tissue and suppression of hemopoiesis . figure (12).

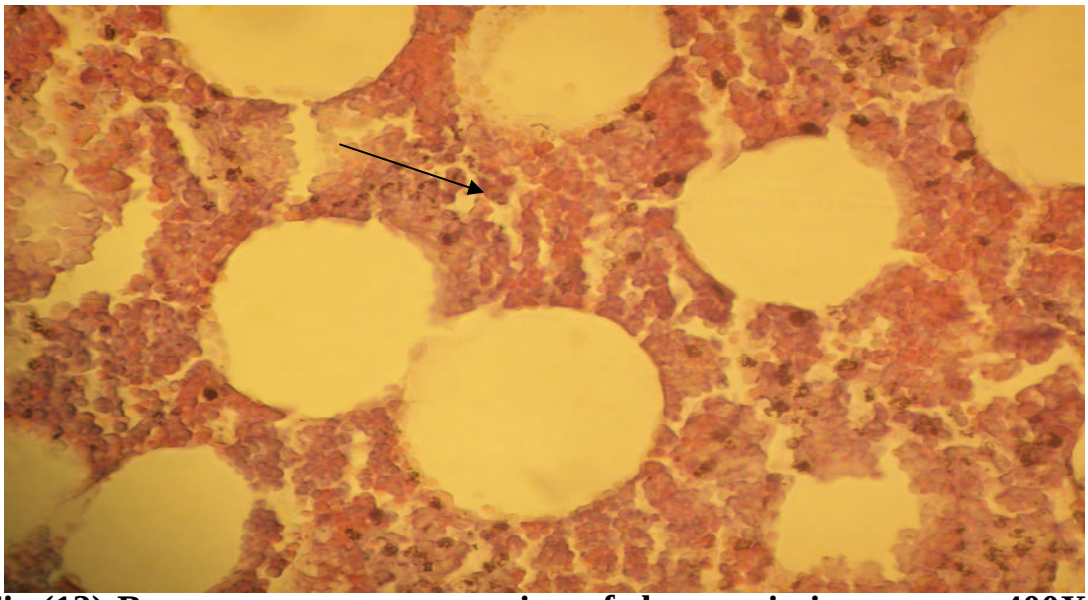


Fig.(12) Bone marrow : suppression of hemopoiesis . 400X (H. and E. Stain)

7- Kidney

There was dilated cortical tubules . figure (10).

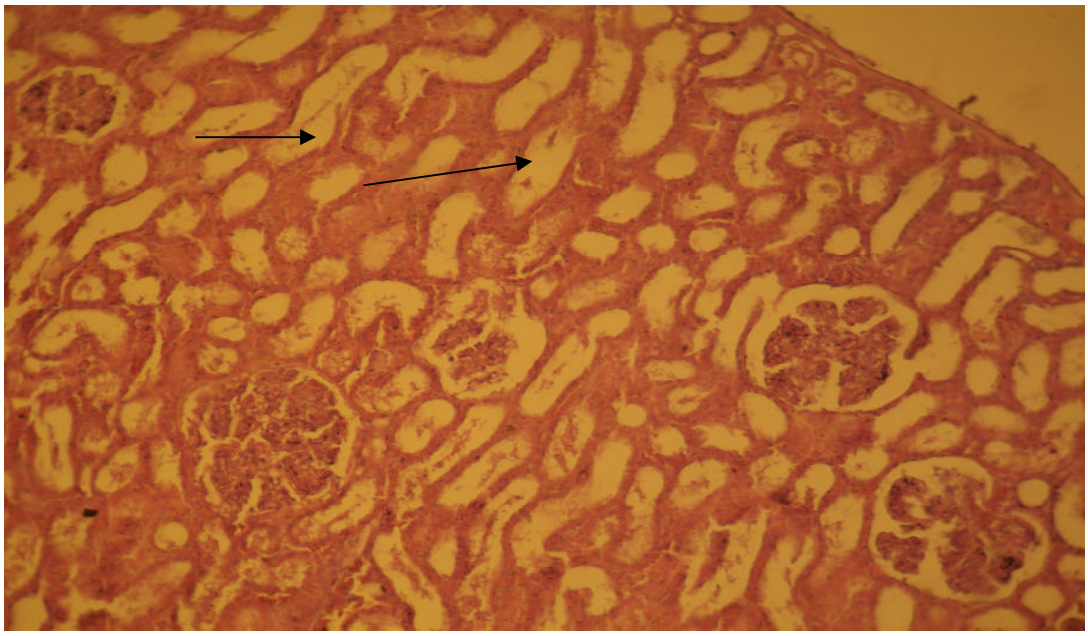


Fig.(13) Kidney : dilated cortical tubules . 100 X
(H. and E. Stain)

8- Respiratory Tissues

The lungs have emphysema and dilated alveoli and there was a folding of the bronchiolar epithelium associated with the proliferation of the epithelial lining as in figure (14) , folding of secondary bronchus epithelium associated with the hyperplasia of epithelium . figure (15).

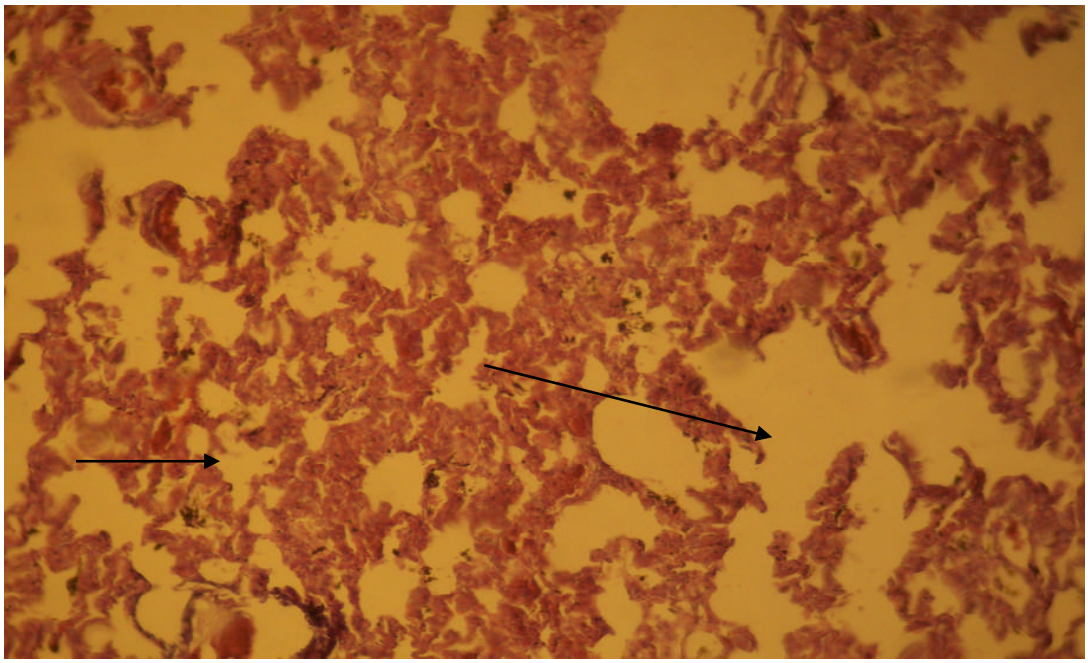


Fig.(14) Lung : emphysema and dilated alveoli , also congestion. 100 X (H. and E. Stain)

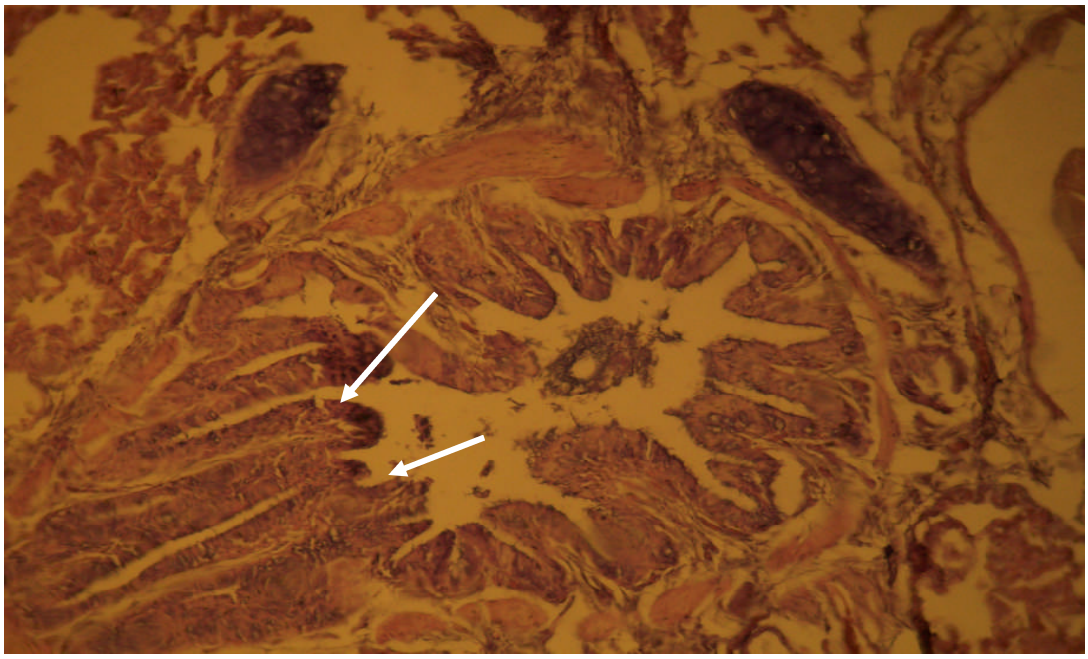


Fig.(15) Lung : folding of Secondary bronchus epithelium associated with the hyperplasia of epithelial . 100 X (H. and E. Stain)

4-2- Results of Acute Experiment (70 mg/kg b.w.) of Cypermethrin

4-2-1- Clinical Signs

After the oral administration of CYP. with a dose of 70 mg / kg b.w. ,the clinical signs which reported involve the following : Head shaking ; this symptom persist for 15 mints after the administration .Lip liking appear immediately and persisting for 20-30 mints .Restlessness continues for about 30 minutes after the oral administration .Diarrhea was reported after 10-12 hours of dosing with a greenish color and normal odor ,the diarrhea persisted until the end of the experiment .

4-2-2- Temperatures , Pulse and Respiratory Rates

There is no significant difference in the means of temperatures between the pre exposure and treating times in all animals .

While, there is a significant increase in the pulse and respiratory rates after the 6 hours of the dosing and the increase persisting until the end of experiment .These results were illustrated in table (4-16) .

Table (4-16) : Means of Temperatures , Pulse and Respiratory Rates . of Sheep Treated with High Dose of CYP.

parameter / Time	Temperatures / Minute Mean ± Standard error	Pulse rate / minute Mean ± Standard error	Respiratory rate/ Minute Mean ± Standard error
Zero Time	a 39.3 ± 0.5	a 85.5 ± 5.2	a 28 ± 1.2
6 hours	a 39.2 ± 0.75	b 100 ± 4.5	b 44 ± 2.3
12 hours	a 39.5 ± 0.25	b 98 ± 4.2	b 45 ± 3.5
24 hours	a 39.0 ± 0.5	b 101.5 ± 5.5	b 47 ± 2.5

* Different small letters mean significant differences among different periods .

4-2-3- Haematological Parameters

There is no significant differences in the haematological parameters which include RBCs count, Hb%, PCV, MCV and MCHC between the pre exposure time and treating times in all animals until the end of the experiment . these values were illustrated in table (4-17) .

Table (4-17) : Haematological Parameters of Sheep Treated with High Dose of CYP.

parameter / Time	Hb g/dl Mean ± Standard error	PCV% Mean ± Standard error	RBCs X 10^{12} cell / L Mean ± Standard error	MCV Mm^3 Mean ± Standard error	MCHC g/dl Mean ± Standard error
Zero Time	a 12.2 ± 0.82	a 35 ± 2.5	a 6.40 ± 0.55	a 54.68 ± 3.51	a 34.85 ± 2.1
6 hours	a 12.5 ± 0.95	a 36 ± 2.8	a 6.35 ± 0.65	a 56.69 ± 3.65	a 34.72 ± 2.3
12 hours	a 12.3 ± 0.75	a 36 ± 2.6	a 6.5 ± 0.75	a 54.72 ± 2.65	a 34.16 ± 2.7
24 hours	a 12.5 ± 0.8	a 38 ± 2.8	a 6.28 ± 0.5	a 55.22 ± 3.8	a 32.89 ± 2.4

*Similar small letters mean no significant differences among different periods .

4-2-4- Biochemical Results

4-2-4-1- Liver Enzymes

There were a significant increase in the liver enzymes which include AST ,ALT ,ALP and LDH at the 6^{th} hours after the inoculation of the animal dosing and this increase continues until the end of the experiment .these values were illustrated in table (4-18) .

Table(4-18):Liver Enzymes of Sheep Treated with High Dose of CYP.

parameters / Time	AST IU / L Mean ± Standard error	ALT IU / L Mean ± Standard error	ALP IU / L Mean ± Standard error	LDH IU / L Mean ± Standard error
Zero Time	a 36.3 ± 3.2	a 28.25 ± 1.5	a 135.68 ± 1.5	a 152.0 ± 4.45
6 hours	b 59.6 ± 2.5	b 42.5 ± 2.3	b 139.7 ± 1.8	b 160 ± 4.3
12 hours	c 92.5 ± 3.5	c 50 ± 2.5	c 165.8 ± 2.3	c 188.5 ± 3.9
24 hours	d 155.5 ± 4.8	d 47.75 ± 2.6	d 168.34 ± 2.5	d 231.75 ± 5.4

* different small letters mean significant differences among different periods .

4-2-4-2- Kidney Functions and Total Protein

There was significant increase in the blood urea nitrogen (BUN) and Creatinine at the 6th hours of the experiment and the increase continues until the end of the experiment .

The T.P. show a significant decrease , these results were illustrated in table (4-19) .

Table (4-19) : Kidney function and T.P. of Sheep Treated with High Dose of CYP. .

parameters / Time	TP g /L Mean ± Standard error	Urea mmol / L Mean ± Standard error	Creatinine µmol / L Mean ± Standard error
Zero Time	a 68.1 ± 1.5	a 2.5 ± 0.15	a 85.2 ± 1.2
6 hours	b 52.2 ± 2.2	b 2.9 ± 0.145	b 91.4 ± 2.5
12 hours	c 42.7 ± 1.2	c 3.45 ± 0.135	c 111.5 ± 3.7
24 hours	d 30.6 ± 1.2	d 5.22 ± 0.140	d 120.4 ± 5.2

* different small letters mean significant differences among different periods

4-2-5- Gross and Histopathological Changes

4-2-5-1- Gross Lesions

The congestion of the subcutaneous and thoracic cavity blood vessels was observed .There was also severe congestion of large and small intestine with the gaseous dilatation of the large intestine . Figure(16). The abomasums was also congested but there was an enlargement of the mesenteric lymph node which appear as cooked appearance .The kidney as especially the cortex appear congested. The spleen has a minimal congestion .The brain was also congested in all parts . Figure(16).

Lungs undergo severe congestion with a gray hepatization and there was large amounts of ooze blood from the cut site , and the trachea have congested .

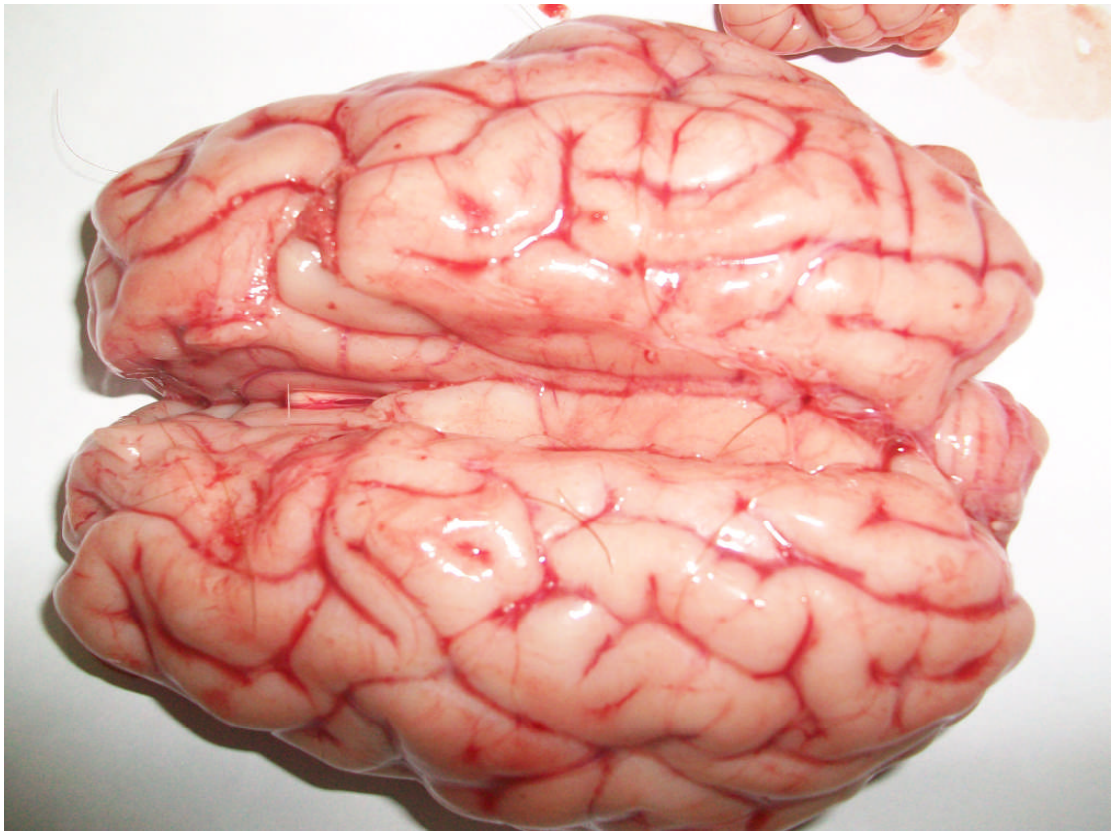


Fig.(16) Brain: Severe congestion .

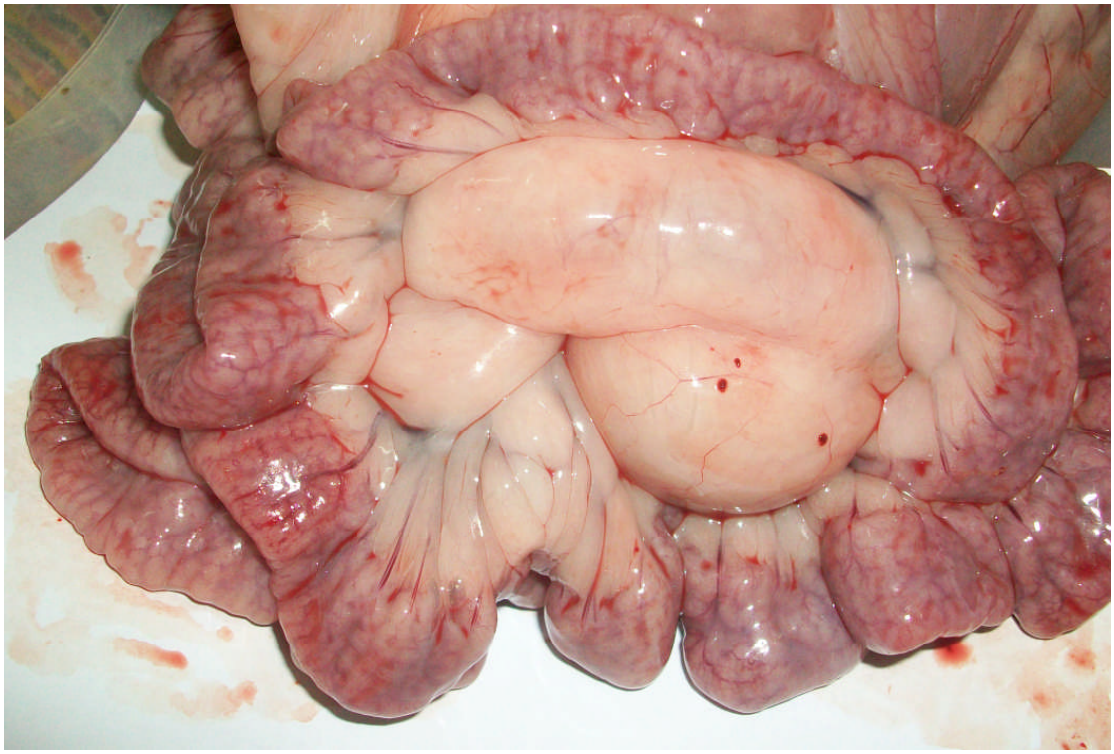


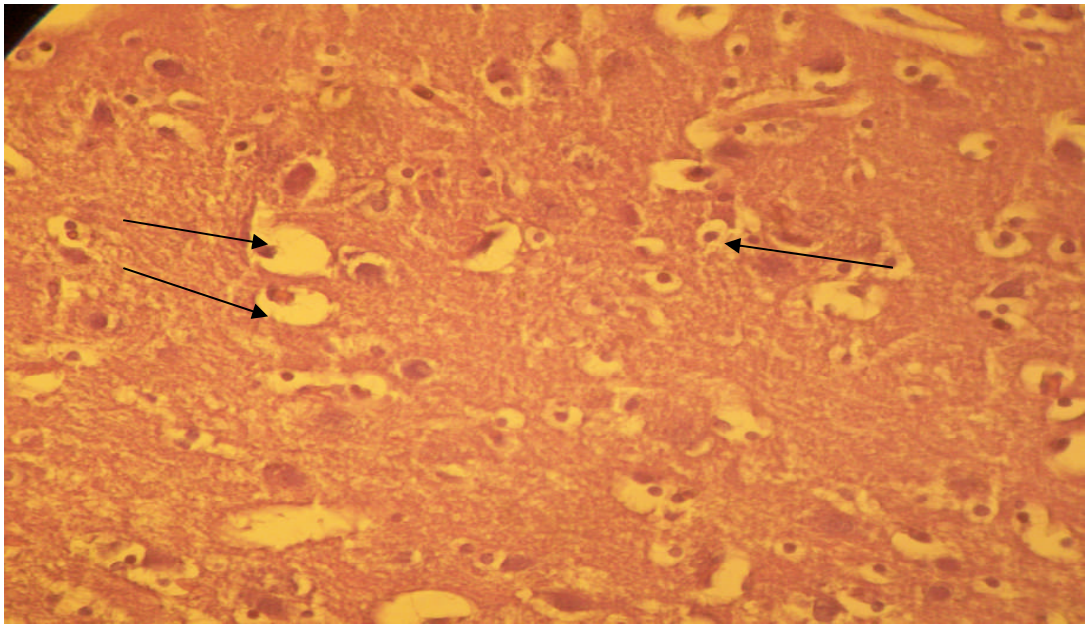
Fig.(17) Intestine : Severe congestion .(Gross Lesion)

4-2-5-2- Histopathological changes

The histopathological examinations revealed that many organs showed changes as following :

1- Nervous Tissues

There was vacuolation of nerve fibers in the white matter of the brain .Also there is a vacuolation of the neuron of the cerebellum . figure (18).Medulla oblongata has a vacuolation of nerve fibers in the white matter . figure (19) .



Fig, (18) Brain, vacuolation of neurons of the white mater .
400 X (H. and E. Stain)

The spinal cord show a vacuolation in different degrees according to its regions, the cervical and lumber regions have sever vacuolation of the whit mater and it is also show a vacuolation of the neuron, while the thoracic region has a vacuolation of nerve fibers in the white mater only . figures (20 and 21).

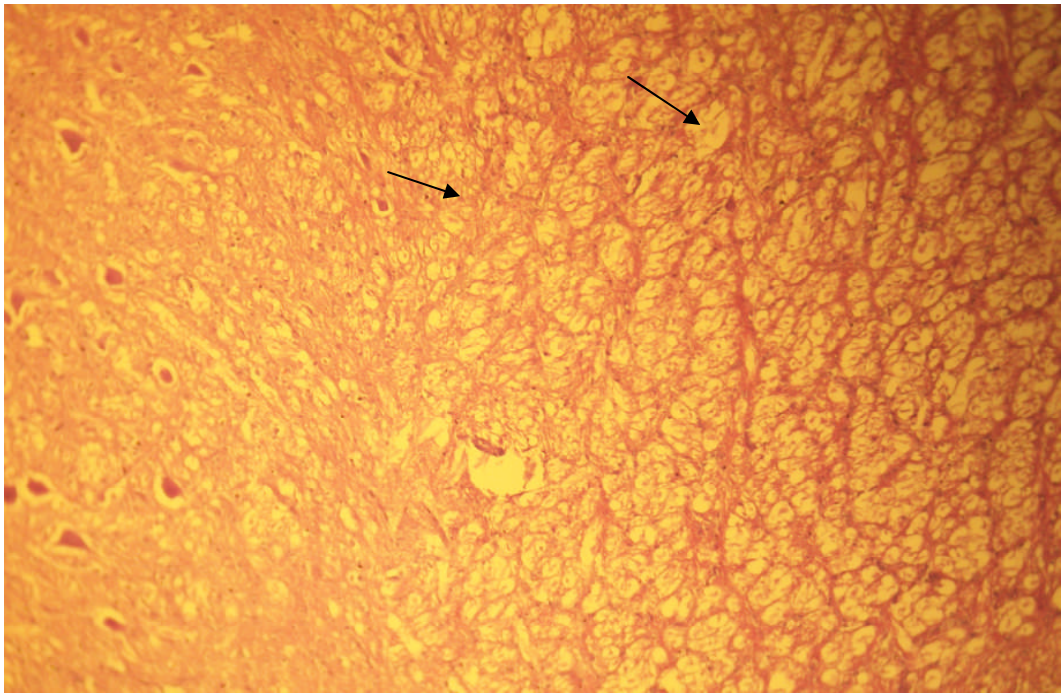
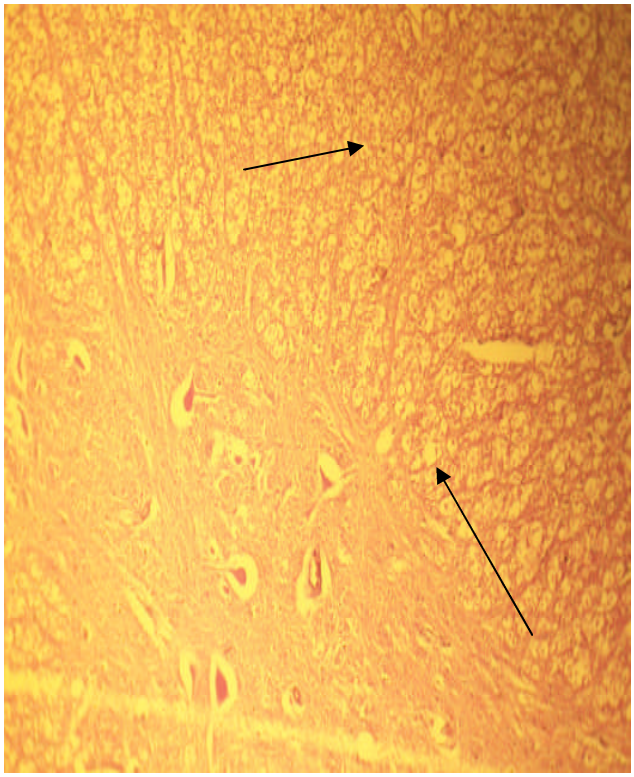


Fig.(19) **Medulla oblongata: vacuolation of nerve fibers of white matter 100 X (H. and E. Stain)**



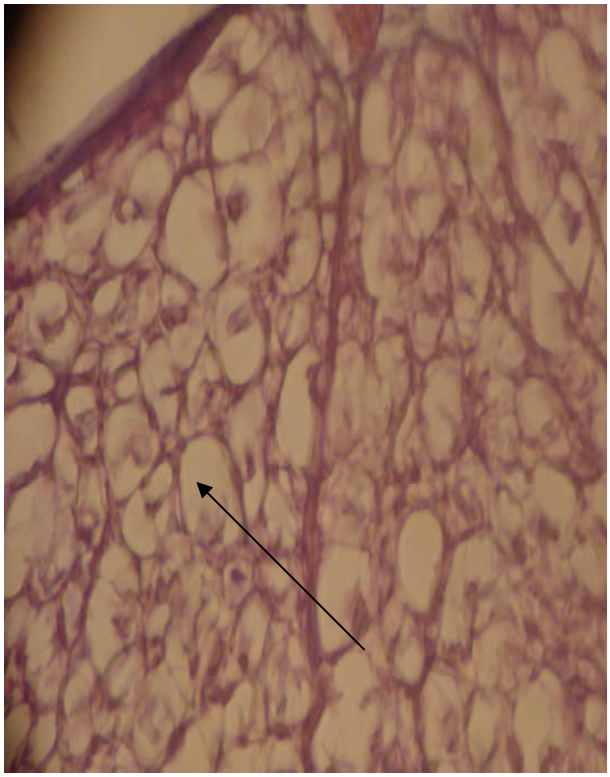


Fig. (20) Spinal cord(Cervical)100X - vacuolation of the white mater (H. and E. Stain)

Fig.(21)Spinal cord(Lumber) 400X

2- Gastro-intestinal Tract

There was minimal vacuolation of the papillary projections – lamina propria of the rumen .figure (22). In the reticulum there was epithelium vacuolation .

In the omasum there was to be sever lyses changes or the epithelium and degenerated .The abomasum was show an increase in the mucosecretion in the upper part of the epithelium .

In the intestine thickening epithelial lining ,the small intestine has a congestion and increase in the cellulararty of the lamina propria while the large intestine show degeneration of the mucosal epithelium tissue with congestion . figure (23).

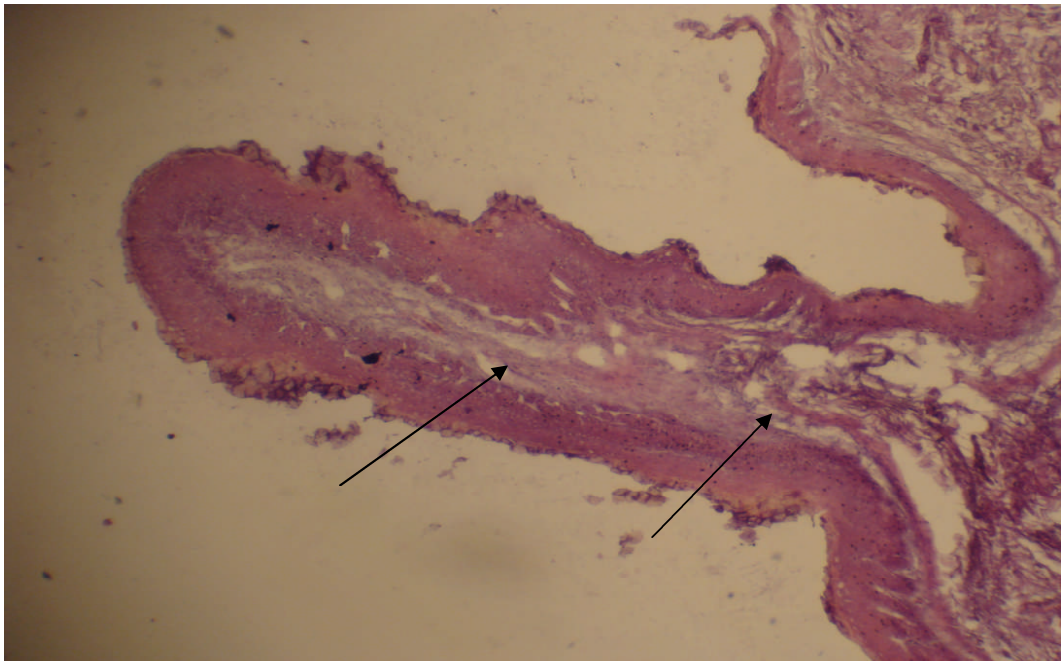
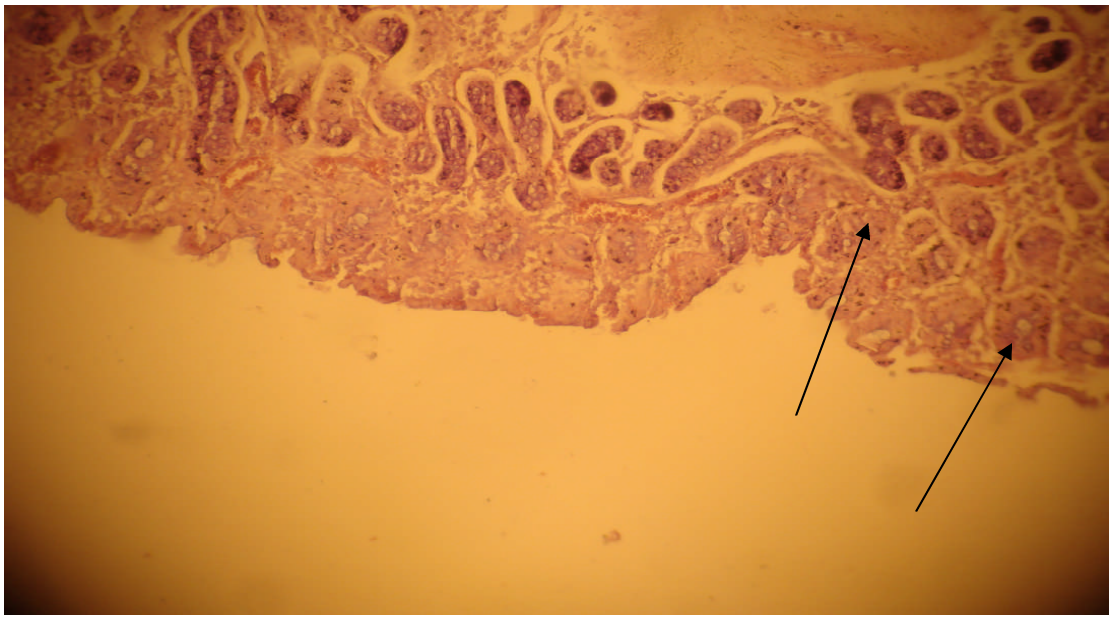


Fig.(22) Rumen : Papillary projection - vacuolation of the rumen lamina propria 40X (H. and E. Stain)



Fig(23) Large intestine appearance the degeneration of mucosal epithelial tissue . 100 X (H. and E. Stain)

3- Respiratory organs

The lungs show a severe congestion and emphysema and the dilated alveoli was present with the submucosal congestion and minimal mucosal epithelium hypertrophy and proliferation congestion was seen in the trachea . figures (24 and 25)

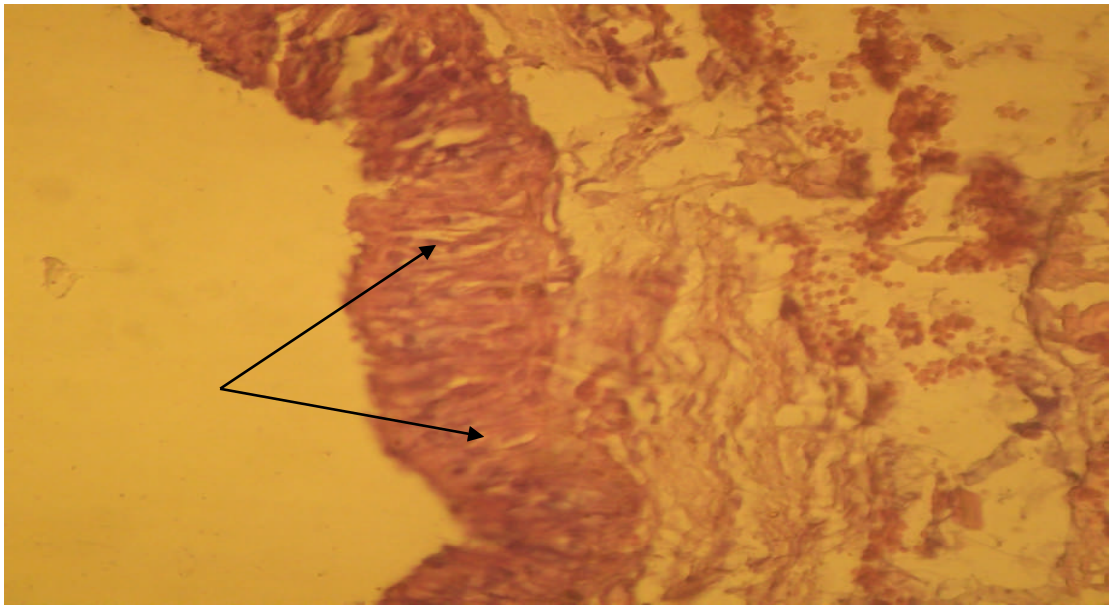


Fig.(24) Trachea : minimal mucosal epithelial Hypertrophy/ proliferation congestion. 400 X (H. and E. Stain)

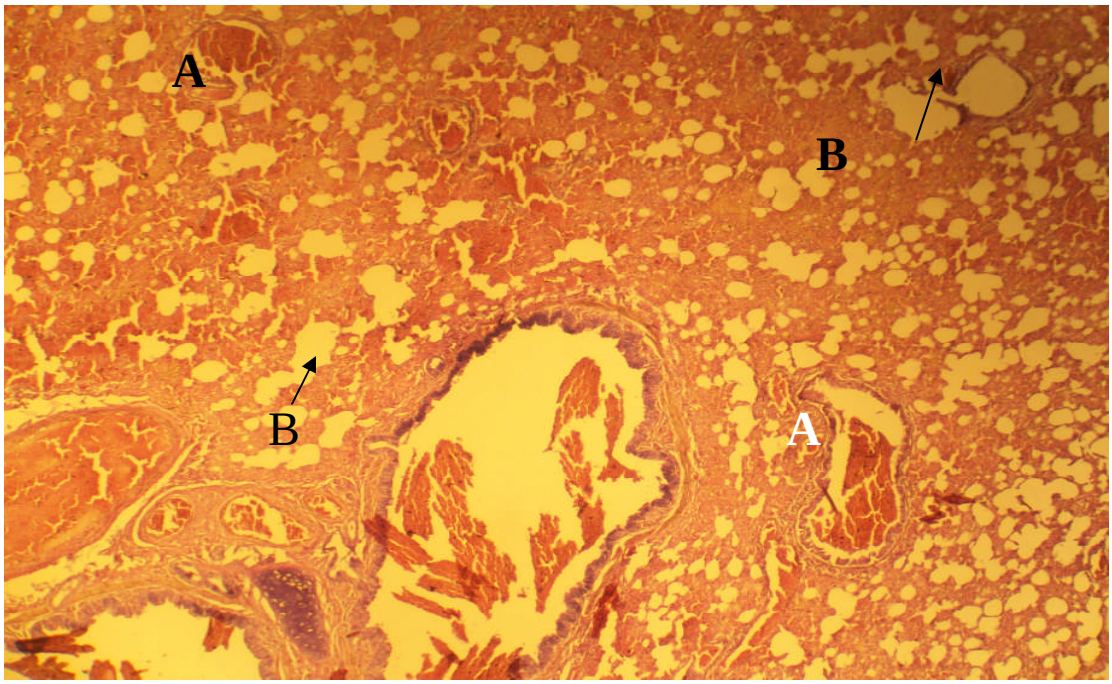


Fig.(25) Lung: A) sever congestion (arrow) B) dilated alveoli (arrow) 40X (H. and E. Stain)

4- Kidney

The kidney was show one clear change which is the dilated of the cortical tubules as much clear in figure (26)

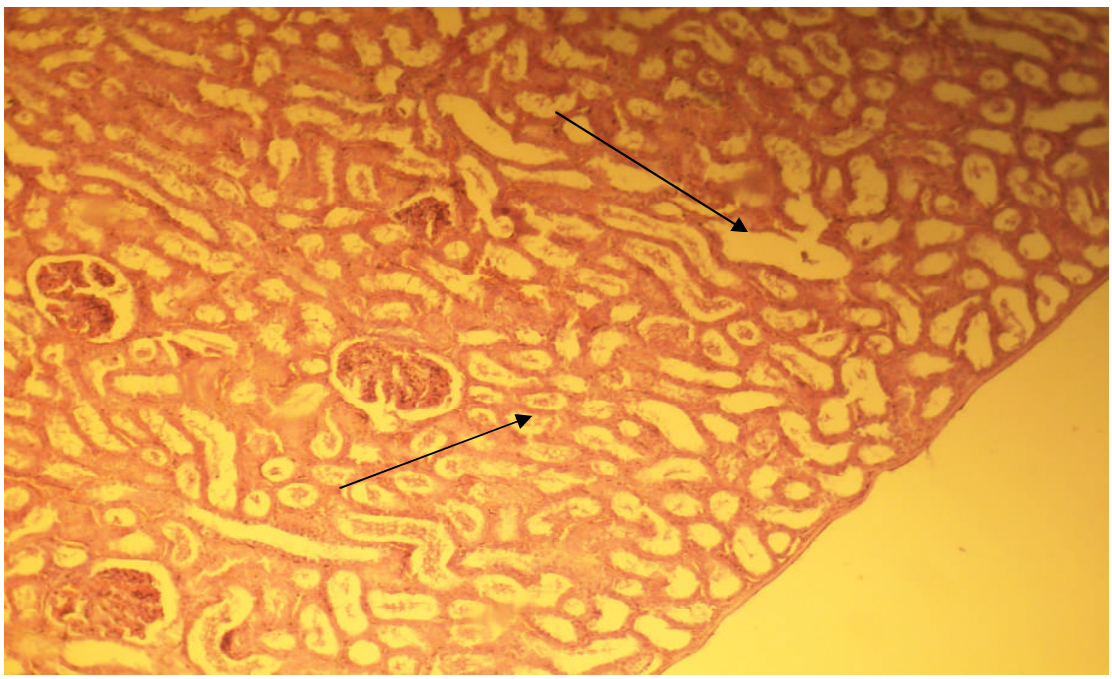


Fig.(26) Kidney dilate cortical tubules 100 X (H. and E. Stain)

5- Liver

There was centerilobular vacuolation of the hepatic cells, minimal periportal fibrosis and congestion (periportal congestion).figure (27)

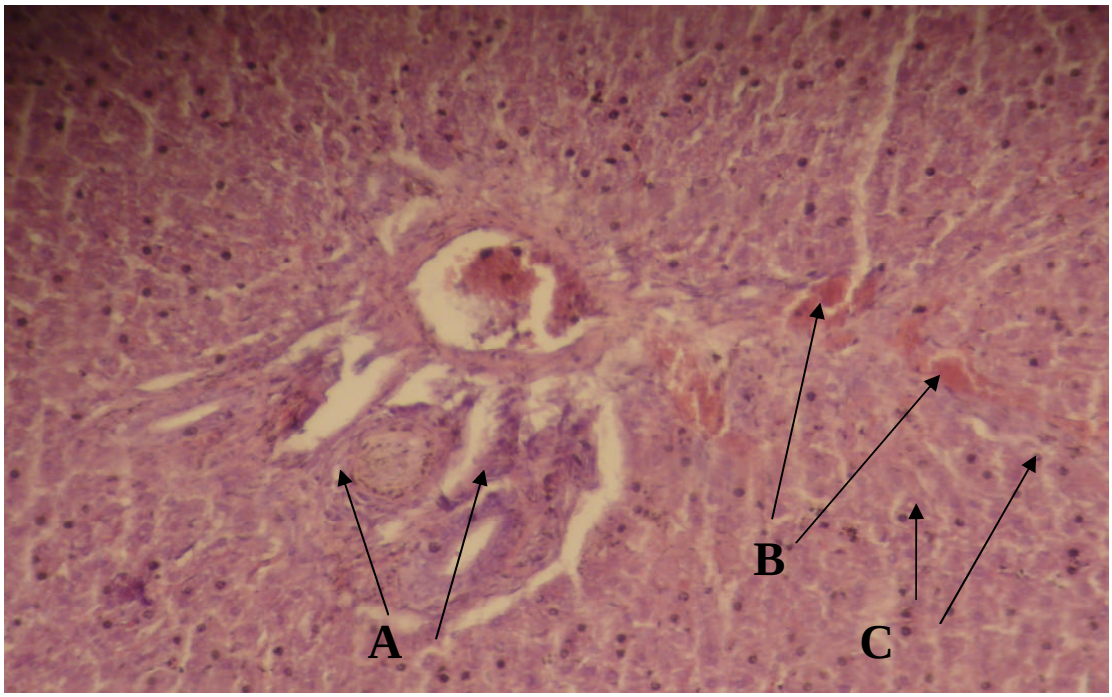


Fig.(27)Liver:A) minimal periportal fibrosis (arrows),B) periportal congestion C) vacuolation .(arrows) 100 X (H. and E. Stain)

6- Bone Marrow

There was prominent adipose tissue suppression of the hemopoisis and the area of RBCs have policythemia . figure (28)

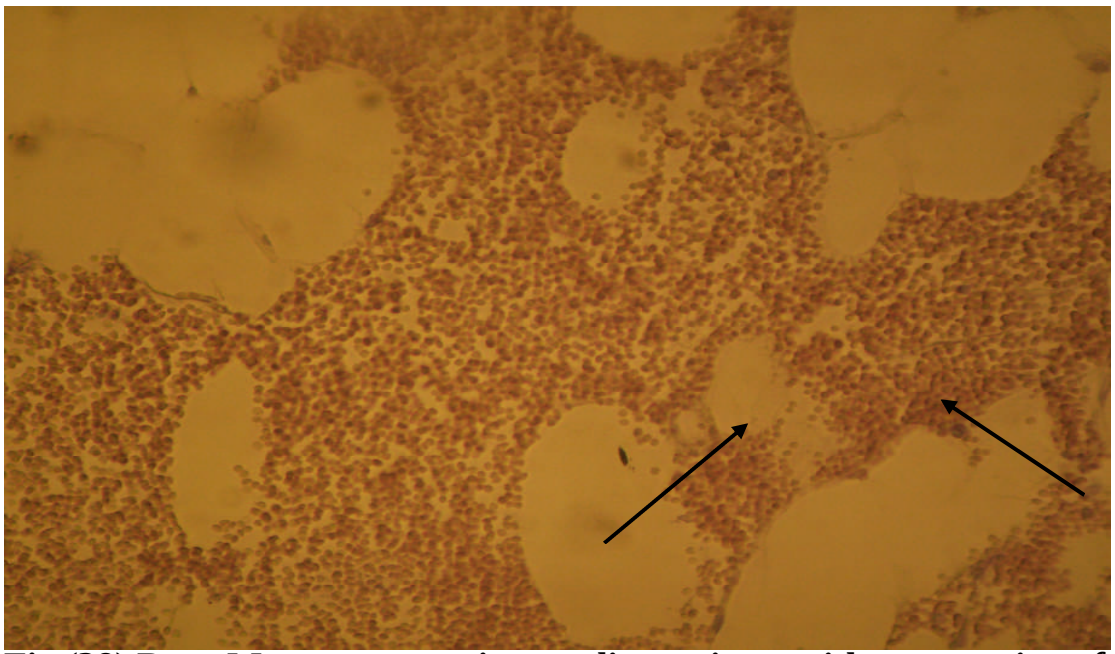


Fig.(28) Bone Marrow : prominent adipose tissue with suppression of haemopoisis . 40X (H. and E. Stain)

Chapter Five

Discussion

5- Discussion

5-1- clinical signs

Head shaking and restlessness observed in the two experiments this signs are due to the toxicity of CYP which delays the closing of sodium channel ; thus increase neuronal plasma membrane excitability by membrane depolarization . there were similar nervous manifestations reported by Tamang *et al*. (1991) and Khan *et al*. (2009) in goats which treated by CYP dipping , as well as Shah *et al.* (2007) showed similar results in rabbits .

However, these results disagree with Flaskos *et al*.(2006) . Flaskos *et al*.(2006) observed no effects of CYP on neuronal cells . The duration of nervous signs corresponding with Kol *et al*. (2007) and Shah *et al*. (2007) , who reported that the nerve stimulation is started after 5-10 minutes and persisting for 30 – 90 minutes .

Lip licking which occurred in the two experiments is due to the CYP physical properties (burning) , and that because of irrition of CYP which causes papules in the skin and congestion or edema which reported by Smith *et al*. (1996) and Tample and Smith. (1996) .Also Krastev *et al*. (2000) mentioned that it occurred due to stomotitis caused by CYP .

Diarrhea in the two experiments probably occurs due to the intestinal mucosal epithelium degeneration and the desquamation of the intestine was reported by Khan *et al*. (2009) . Diarrhea may be due to the degeneration and vacuolation of the nerves which stimulate to cause diarrhea .

In both experiments there was no significant differences in the body temperatures of the treated animals and there were increases in respiratory and pulse rates ,these results were in agreement with Yousef

et al. (1998) , the increase in respiratory and pulse rates are due to reducing of RBCs count , Hb% and PCV in the low dose of the experiment . Besides the histopathological changes of the lungs (emphysema) can be explain these results in both low and high dose experiments .

5-2- Haematological Parameters

In the high dose of CYP experiment, there is no significant differences in the treated group in blood parameters (RBCs count , Hb% , PCV , MCV and MCHC). These results are disagreed with Yousef *et al*. (1998) in sheep and Khan *et al*. (2009) in goats ;they reported differences in these parameters. .

Also Yousef *et al*. (2003) Shah *et al*. (2007) and [a]Ahmad *et al*. (2009) reported similar results in rabbits ,this difference in the results may be due to the shorter time of the high dose experiment while in low dose experiment shows : a decrease in the RBCs count, Hb% and PCV, similar results were reported by Yousef *et al*. (1998) and Khan *et al*. (2009) in sheep ,Yousef *et al*. (2003) and Shah *et al*. (2007) in rabbits , all those researchers explain that red blood cells break down due to the toxic effects of CYP on the bone marrow or may be due to hyperactivity of bone marrow which leads to the production of red blood cells with impaired integrity which are easily destroyed in the circulation by reticulo-endothelial system Shah *et al*. (2007) .

There is no change in MCV and MCHC ; this corresponding with similar results in Shah *et al*. (2007) in rabbits , this result indicates that there is normocytic normochromic anemia .

5-3- Biochemical Examinations

The study shows that there is a significant increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) , alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) this result which agreement with Yousef *et al*. (1999) in sheep, Khan *et al*. (2009) in goats, Seth *et al*. (2000) in rabbits , Jagvinder *et al*. (2001) in buffalo calves , they explain that elevation of these enzymes occurs due to the hepatocytes injury ,but the activities of these enzymes in blood plasma can be used as relevant stress indicators .while these results are disagreement with Yousef *et al*. (1998) and Krastev *et al*. (2000) in sheep and Kol *et al*. (2007) in women .

Also Khan *et al*. (2009) explain that the increase of both transaminases by indicated amplified transamination process ,this is due to amino acid that undergoes biodegradation in order to cope with the energy .

ALP and LDH in the present study show significant increase due to the liver damage or the impaired liver function as well as oxidative tissue damage Krastev *et al*.,(2000) and Khan *et al*. (2009) .

Blood urea nitrogen and creatinine were show significant increase in the low and high dose of experiments that indicating kidney function is abnormally distress . This is explained by the histopathological changes (dilatation of cortical tubules) . These results did not correspond with Krastev *et al*. (2000) who report that is a decrease in the creatinine in similar studies in sheep .Whereas Yousef *et al*.(2003) reported results occur in sheep kidney similar to those in rabbits .

The total protein (T.P) in the both experiments show a significant decrease . This results is agreement with Yousef *et al*.(1998) in sheep and

Khan *et al*. (2009) in goats .The decrease in T.P due to the defect in the protein metabolism or due to histopathological changes of the liver , kidney and intestine .

The defect in the metabolism of the protein and free amino acids and their synthesis in the liver may be one of the causes of these decreasing .this result is disagreed with Krastev *et al*. (2000) .

In general this decrease may be due to the loss of the protein either because of reduced protein synthesis or by increased protolytic activity or the degradation of the protein .(Yousef *et al*.,1998 ; Khan *et al*.,2009).but Yousef *et al*. (1998) and [a]Ahmad *et al*. (2009) added the excessive losses of protein through the nephrosis as one of the causes ; but [a]Ahmad *et al*. (2009) explain that it occurs due to the pesticide which is disturbs the protein synthesis .

5- 4 - Gross Lesions

In the two experiments the gross lesions which include : the congestion of the most organs in the body this is probably due to the stress factors and the alterations of blood parameters .

CYP is lipophilic in nature (in the brain it can cross the blood brain barrier and enter into systemic circulation) . CYP induces an alteration in the plasma membrane producing increased lipid peroxidation and reduction of fluidity in the hydrophilic region of the plasma membrane bilayer where this pyrethroid is preferred . Therefore , most of body organs appear as congested . (Khan *et al*. 2009)

Also the congestion of the lungs , trachea and brain is due to the physiological responses because the reduction of RBCs and Hb% which leads to cells hypoxia then the body act to increase the amounts of blood in these vital organs to correct this abnormality .

The enlargement of the kidney in the low dose of experiments is due to the dilation of the cortical tubules of the kidney as in the histopathological changes .The ooze blood in the cut sites of the liver and lungs in the low dose in the lungs in the high dose experiments is due to the sever congestion of this organs .

The dark color of the spleen when given a low dose of CYP is because of the excessive damage of erythrocytes as a results of the aromatic amine toxicity and the secondary erythrocytes toxicity and sequestration of the damaged erythrocytes in splenic sinusoids .(Yousef *et al*.,1999).

5-5- Histopathological Changes

The histopathological changes of the CNS and PNS in the two experiments are due to the mechanism of action of CYP which it's act mainly on CNS and PNS .this is agreement with Yousef *et al*. (1999) who explain that by swelling myelin sheath and breaking of some of the axons of sciatic nerves .

In the both experiments there were histopathological changes in the gastro – intestinal tract ,this changes are probably due to the direct irritation of CYP on this organs . this supported by Tample and Smith. (1996) and Smith *et al*.(1996), Beyrbach (2000) and Adriana *et al*. (2004).

While the increase of the muocosecretion in the upper part of intestinal epithelium and proliferation of mucous glands this probably occurs to protect the intestine lining and equivalent the irritation action of CYP which is explain above .All this is agreement with Khan *et al*. (2009) where showed variable degrees of epithelial desquamation of intestinal villi in all the treated group of goats .

The liver shows lobular vacuolations and fibrosis of the peripheral region in the both experiments ,this results is agreement with Yousef *et al*. (1999) , Krastev *et al*. (2000) in sheep and Khan *et al*. (2009) in goats . the necrosis and vacuolation are due to CYP metabolized in the liver via the hydrolytic ester cleavage and oxidative pathway by the microsomal enzyme system (Robert,1987 ;Tamang *et al*.,1991 ; Tample and Smith., 1996 ; WHO,1996 ; Beasly *et al*.,1999 ; Carn *et al*., 2007) this will cause an oxidative stress by reducing the activity of superoxid dismutase and glycogen levels leading to a hepatic degeneration and necrosis .

Also Khan *et al*.(2009) explain that the degeneration of hepatocytes in the peripheral zone occurs because of the influence of toxic compound in the digestive tract .

But in the high dose of CYP there is a lymph node changes is due to increase the total leukocyte count because of the septicemia (Khan *et al*.,2009) .

In the low dose experiment there was histopathological changes in the testes ,these changes is agreement with Yousef *et al*. (1999) in sheep and [b]Ahmad *et al*. (2009) in goats ,this due to the toxic effects of CYP which depend on the dose and duration of the exposure to CYP .

The heart shows changes in the low dose of CYP. and this result disagreement with Yousef *et al*. (1999) . these changes are probably due to the stress which occurs on the heart by increasing heart rate due to the decrease RBCs count ,Hb% and PCV .

The results of histopathology of respiratory organs (lungs and trachea) in both experiments is agreement with Khan *et al*.(2009) , the damaged alveoli was due to the stress of the respiration which appear by the increase in the respiratory rate as explained above .

While the kidney changes in the two experiments are disagreement with Yousef *et al*. (1999) and it's corresponding with Krastev *et al*.

(2000) in sheep and Khan *et al*. (2009) in goats .It may be due to the hyperactivity of the detoxication of CYP . The dilatation of cortical tubules due to it's filling with protein casts (Khan *et al*.,2009)

Bone marrow changes in the two experiments is probably due to the hyperactivity (polycythemia) to correct the reduction of blood cells .

Chapter Six

Conclusions and Recommendations

6- Conclusions and Recommendations

6-1- Conclusions

1- Cypermethrin is somewhat safe for use in the treatment of ectoparasites in sheep .
2- Cypermethrin causes only minimal changes in the vital organs and mild clinical signs which disappear spontaneously .
3- Cypermethrin causes anemia in repeated doses (daily doses for 63 days) .
4- Cypermethrin causes reproductive disturbances in male sheep through the long oral exposure .

6-2- Recommendations

1- Conduct a study to evaluate the toxicity of CYP in cattle , goats and horses .
2- Comparative study among the members of pyrethroids to choose the more safe antiectoparasites for use in animals .
3- Comparative study between CYP and organophosphorouse compounds to determine the more safe of it .
4- Careful use of CYP at the reproductive seasons of sheep .

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الخلاصة

أجريت هذه الدراسة لغرض تحديد تأثيرات السيبرمثرين على العلامات السريرية وبعض المعايير الدمية والكيموحيوية والتغيرات النسجية المرضية في الأغنام العرابية .

قسمت الدراسة إلى قسمين : الأول ؛ جرعة فموية منخفضة من السيبرمثرين بمقدار ١٧ ملغم / كغم/وزن الجسم / باليوم ، أعطيت لـ ٤ أغنام (مجموعة T) بينما تم استخدام ٤ أغنام أخرى كمجموعة ضبط (مجموعة C) للدراسات المقارنة .

العلامات السريرية تمت ملاحظتها يوميا بينما جمع الدم والمصل كل ١٥ يوم للدراسات الدمية والكيموحيوية . وكانت النتائج المسجلة عدم وجود اختلاف واضح في معدل الحرارة ($P>0.01$) بينما كان هنالك زيادة واضحة في معدلات النبض والتنفس ($P<0.05$) ولم تأشر اختلافات معنوية في معدل الحجم ألكريي ومعدل تركيز خضاب الدم ألكريي .

بينما كان هناك نقصان واضح في حساب عدد كريات الدم الحمراء وتركيز خضاب الدم وحجم الدم المضغوط والبروتين الكلي ($P<0.05$) في مجموعة T وكانت هناك زيادة واضحة في إنزيمات الكبد : اللاكتيت ديهايدروجينيز و الاسبارتيت امينو ترانسفيريز والالنين امينوترانسفيريز والالكلاين فوسفاتيز وأيضا في وظائف الكلية: تركيز يوريا الدم والكرياتينين ($P<0.01$) في مجموعة T .

ثم بعد ٦٣ يوم من المعالجة قتلت حيوانات المجموعة T لأجل الدراسات العيانية والنسجية المرضية وكانت النتائج كما يلي : وجود احتقان للأوعية الدموية تحت الجلد و الأمعاء و الكلية و الطحال (الذي يظهر ذات لون اسود غامق) والكبد و الأوعية الدموية المساريقية والأوعية الدموية في للتجويف الصدري والرئتان التي تحوي تكبد رمادي والدماغ و القصبة الهوائية .وكان هناك توسع في العقد اللمفاوية المساريقية والكليتين وكيس المرارة الذي يحوي سوائل خفيفة وداكنة كافات عيانية .بينما وجدت تغيرات نسجية مرضية في الدماغ و المخيخ والنخاع المستطيل والحبل ألشوكي والكرش والمعدة الرابعة والأمعاء الدقيقة والغليظة والرئتان والقصبة الهوائية والكلية والكبد والخصيتان والقلب ونخاع العظم .

أما في الجزء الثاني تم إعطاء جرعة منفردة عالية من السيبرمثرين بمقدار ٧٠ ملغم / كغم وزن الحيوان لـ ٤ حيوانات ، العلامات السريرية تم ملاحظتها أما الدم والمصل تم جمعها في التجربة بالأوقات قبل التعرض و٦ و١٢و٢٤ ساعة ، تمت مقارنة الفترات ما بعد المعالجة مع تلك قبل المعالجة في الدراسات الدمية والكيموحيوية حيث أشارت النتائج إلى ما يلي :لم

الخلاصة

يوجد اختلاف واضح في معدل درجات الحرارة وحساب كريات الدم الحمر وتركيز خضاب الدم وحجم الدم المضغوط ومعدل الحجم ألكريي ومعدل تركيز خضاب الدم ألكريي ما بين زمن قبل التعرض وزمن المعالجة في جميع الحيوانات حتى نهاية التجربة .بينما لوحظت زيادة واضحة في معدلات النبض والتنفس وإنزيمات الكبد التي تشمل : الاسبارتيت امينوترانسفيريز والالنين امينوترانسفيريز والالكلاين فوسفاتيز اللاكتيت ديهايدروجينيز بين زمن قبل المعالجة وزمن المعالجة في جميع الحيوانات حتى نهاية التجربة. ولكن كان هناك تناقص واضح في البروتين الكلي .

تم قتل الحيوانات في نهاية التجربة لغرض دراسة التغيرات العيانية والنسجية المرضية وكانت النتائج كما يلي : وجود احتقان في الأوعية الدموية في التجويف الصدري والأوعية التحت جلدية ،احتقان حاد للكبد والدماغ بينما تعرضت الرئتان باحتقان حاد يتميز بتكبد رمادي ،المعدة الرابعة والأمعاء الغليظة والدقيقة يصاحبها توسع غازي في الأمعاء الغليظة وتوسع العقد اللمفاوية المساريقية كافات عيانية .

بينما تمت ملاحظة تغيرات نسجية مرضية في الدماغ (المخيخ) والنخاع المستطيل والحبل ألشوكي في كل مناطقه و الكرش والشبكية والمعدة الرابعة والأمعاء الغليظة والرئتان والقصبة الهوائية والكلية والكبد ونخاع العظم .

دراسة سريريه لسمية السايبرمثرين في الأغنام العرابية

رسالة مقدمة إلى

مجلس كلية الطب البيطري_جامعة البصرة

وهي جزء من متطلبات نيل درجة الماجستير في علوم الطب البيطري

(الطب الباطني و الوقائي)

تقدم بها الطالب

حسنين هشام ناصر العطيش

بكالوريوس طب وجراحة بيطرية

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بـأشـــراف

أ. م. د. رحمن كاظم محسن

أ. م. د. إسراء عبد الودود السعد

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